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CONGENITAL INFECTION OF THE LUNGS, MIDDLE EARS AND NASAL ACCESSORY SINUSES

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The problem of infectious disease of the respiratory system in newborn infants has been considered in medical literature for more than thirty years and there is still some diversity of opinion regarding both causes and manifestations. Any one who has done even a moderate number of autopsies on infants is acquainted with the fact that the respiratory system is frequently the site of pathologic changes which are contributory to, or solely responsible for, the death of the child. The lungs have been carefully studied, but related structures have too often been neglected, with the result that there is a lack of substantial proof for the theories that have been advanced as to the origin and mode of infection. Congenital pneumonia has been discussed often in the literature, congenital sinusitis has been mentioned briefly, disease of the pharynx and larynx has been considered in connection with anomalies of structure, and congenital otitis media has received slight attention as an inflammation resulting from aspiration of infected amniotic fluid.

Gomperez [1] in 1906 suggested that both pneumonia and middle ear infection in the newborn might be due to aspiration of infected amniotic fluid. In 1914 Hess Thaysen,[2] reporting on pneumonia in infants, suggested four possible modes of infection, as follows: (1) infection through the placenta; (2) infection due to aspiration of material from the uterus or birth canal or to aspiration of food or of secretions in the nose and mouth of the baby after birth; (3) aerogenous infection after birth, and (4) metastatic infection from a primary focus in some other part of the body. The majority of the more recent writers agree that inflammatory processes in the various parts of the respiratory system in stillborn and liveborn infants are most often due to aspiration of infected material, which may come from the uterus or elsewhere (Hess Thaysen's second mode).

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1. Gomperez, B.: Pathologie und Therapie der Mittelohrentzündungen im Säuglingsalter, Vienna, Joseph Šafář, 1906.

2. Hess Thaysen, T. E.: Jahrb. f. Kinderh. **79**:140, 1914.

Johnson and Meyer [3] reported in detail on the significance of normal and infected amniotic fluid in the lungs of infants. The recognition of the fluid itself is extremely difficult, but one may identify with relative ease those more solid elements normally suspended in the fluid. Cornified epithelial cells are the most constant and characteristic evidence of the presence of amniotic fluid. Vernix caseosa, lanugo hairs and meconium, when it is present, are equally characteristic though somewhat more difficult to identify in routine sections. The finding of any or all of these solid elements constitutes the means of identification of amniotic fluid in any location. As Johnson and Meyer [3] stated, the entire respiratory tract is continuous with the amniotic cavity throughout fetal life, and the nose, mouth and pharynx are washed by the fluid. Since the nasal sinuses and middle ears are continuous with the nasopharynx, they must also be penetrated by the fluid. It is still uncertain whether or not fetal respiratory movements normally allow amniotic material to enter the trachea and bronchi, or whether these movements may take place with a closed glottis, so that the amniotic fluid found in the lungs is merely that drawn in from the pharynx at the time of the first inspiration after birth. Ordinarily, variable amounts of epidermal cells and vernix caseosa are found in the middle ears and nasal sinuses, and only minimal quantities appear to reach the atelectatic alveoli of the lungs.

Large amounts of amniotic material in the respiratory tract are doubtless indicative of a certain amount of fetal asphyxia, which may have been caused by true knots in the cord, excessive contractions of the uterus or insufficiency of placental circulation. Massive accumulations of fluid and solid material may interfere with the normal function of the lungs after birth and result in death by asphyxia. Because the sinuses and ears are not necessary for life at this period, heavy accumulations of foreign material in these structures are probably not significant. There is, however, a distinct and interesting parallelism between the amounts of amniotic fluid found in the ears and sinuses and the amounts found in the lungs, indicating that asphyxia with forced intrauterine respiration tends to drive more of this material into all portions of the system.

Since there is so often no evident reaction to the amniotic elements, many investigators have assumed that these elements are not irritating. Johnson and Meyer [3] reported the presence of epidermal cells in the lungs several days after birth with no evidence of inflammation, and Farber and associates [4] expressed the belief that there is normally no reaction to these substances. It is probable that in the healthy infant there is a gradual physiologic removal of foreign material during the first few days of life. Warwick [5] and Hemsath [6] investigated the lungs and

3. Johnson, W. C., and Meyer, J. R.: Am. J. Obst. & Gynec. **9**:151, 1925.
4. Farber, S., and Sweet, L. K.: Am. J. Dis. Child. **42**:1372, 1931.
5. Warwick, M.: New York State J. Med. **37**:2075, 1937.
6. Hemsath, F. A.: Arch. Otolaryng. **23**:78, 1936.

ears of newborn infants, respectively, and although both of these authors found in some cases no evidence of reaction, both reported the presence of purulent exudate surrounding amniotic material. In some of their cases no bacteria could be demonstrated, and therefore they stated that epidermal cells, vernix caseosa and bile salts may set up a foreign body reaction with leukocytic infiltration even in the absence of infection. Hemsath [6] quoted Aschoff as distinguishing between the so-called otitis media of the newborn and purulent otitis media of infancy, the former being considered to be the result of contamination by nonspecific impurities aspirated in the uterus.

If the amniotic fluid is contaminated by bacteria, it is easy to see that inflammatory processes may be set up wherever this material penetrates, and the finding of leukocytic exudates would be expected in all parts of the respiratory system and in the middle ears. When bacteria are seen and identified, the diagnosis is certain, but their apparent absence may be due only to the smallness of the number present and the difficulty of identifying them in sections. Helwig [7] and Johnson and Meyer [8] mentioned the unsatisfactoriness of bacterial studies in their cases and postulated that at the time of birth antiseptics, such as lysol, might pass through the vagina and into the amniotic cavity, where an irritative reaction might be initiated by the chemical. These authors also discussed the possibility that infected or chemically contaminated material in the vagina might be aspirated by the infant at the time of passage through the birth canal. Inflammatory reactions resulting from chemicals show no specific histologic characteristics and therefore cannot be identified in stained sections. Cases in which a heavy exudate was found in the lumens of the sinuses, ears and lungs without stromal or mucosal reaction force one to consider that a previously infected, bacteria-free amniotic fluid may have been drawn into the respiratory system. Such a fluid might be purulent but contain no living organisms and act merely as an irritant after its aspiration.

It is obvious that neonatal death may result from any interference with aeration of the lungs. The presence of large quantities of amniotic fluid may constitute such an interference, and lungs packed with epidermal cells and vernix cannot function normally. In some cases there is evidence that respiration has been attempted, as the vernix appears to have been forced against the alveolar walls, where it lies as a membrane and forms a barrier to gaseous exchange. The presence of such a vernix membrane—"hyaline membrane" of Johnson and Meyer [3]—must certainly be recognized as a cause of asphyxia and early death of the infant.

In cases in which there are severe congestion and hemorrhage in the lung, it may be impossible to be certain whether the congestion

7. Helwig, F. C.: Am. J. Obst. & Gynec. **26**:849, 1933.

alone caused asphyxia or whether there was associated infection. Congestion and hemorrhage may result entirely from circulatory disturbances, from asphyxia or from early inflammation, and combinations of any or all of these states make it difficult to interpret the findings. In such cases the presence of parallel inflammation in the ears and sinuses may aid in accurate diagnosis of pneumonia, since infected amniotic material penetrates the entire respiratory system and otitis media or sinusitis may not be obscured by hemorrhage. Whenever there is severe congestion, there is apt to be hemorrhage, since the fragile vessels of the newborn infant are unable to withstand much strain.[8] Large quantities of leukocytes in the alveoli of the lung certainly interfere with aeration, and when present at the time of birth they make it impossible for the infant to take even a single effective breath. Thus, the presence of leukocytes in the alveoli of infants dead at birth or immediately thereafter is evidence of inflammation occurring during intrauterine life. If, however, the infant lives for several hours or a day or two, one must consider the possibility of infection occurring at the time of birth. The condition of the infant at birth, the length of life and the type of pneumonic reaction seen after death must all be evaluated in determining the time and source of infection. It is generally agreed that an infant becoming infected during delivery will appear normal at birth, gradually show signs of illness and die in two, three or four days. Therefore infants born in poor condition who die before or during the second day of life and show advanced pneumonia can be considered to have been infected before delivery, with the amniotic fluid as the probable source of contamination. Associated parallel inflammation of the sinuses and ears is further evidence of antenatal infection due to aspiration of contaminated amniotic fluid.

The present study was undertaken for the purpose of investigating and correlating the conditions found in the sinuses, middle ears and lungs of liveborn and stillborn infants. An analysis of the findings in these various locations should aid in establishing the physiologic and pathologic significance of the aspiration of amniotic fluid. I believe that the presence of parallel inflammatory reactions in lungs, ears and sinuses is good evidence that aspiration of irritative material is the direct cause of such inflammation. Since the amniotic fluid is a constant potential vehicle for irritative or infectious material, this fluid must be considered as the usual carrier of such substances.

MATERIAL

The cases included in this series are as nearly consecutive as possible, only those in which the material was macerated having been specifically omitted. Sections of lungs, nasal sinuses and middle ears were examined in every case.

8. Browne, F. J.: Brit. M. J. **1**:469, 1922.

The sections of lungs were obtained at the autopsy table, fixed in Zenker's fluid, embedded in paraffin and stained in the routine manner. Sections of sinuses and ears were prepared by a special technic: After removal of the brain, the entire caput was fixed in solution of formaldehyde U. S. P. and decalcified in 5 per cent nitric acid; the desired regions were sectioned with a large knife in serial frontal blocks about 2 to 3 mm. thick; these blocks were embedded in paraffin, and sections were cut and stained. Hematoxylin–eosin staining was used in all cases, and Gram's stains were made whenever there was leukocytic infiltration.

HISTOLOGIC DESCRIPTION OF NORMAL LUNGS, SINUSES AND EARS OF THE NEWBORN

Histologically, normal lungs of newborn infants (fig. 1 *A*) vary from those of adults only in the fact that the alveolar walls appear thick in relation to the alveolar spaces. This appearance is due to incomplete expansion of the alveoli and consequent failure of the aveolar lining and stroma to have reached any considerable degree of flattening and stretching. There is an apparent tendency to dilatation of the capillaries as well. In premature infants a border layer of cuboid cells may also be seen lining the alveoli.

Histologically, the nasal sinuses in the infant are similar to those in the adult (figs. 1 *B* and 2 *A*). There is a lining layer of ciliated pseudostratified columnar epithelium continuous with the nasal epithelium; underlying the ciliated epithelium is a discontinuous indefinite basement membrane, and below the basement membrane is the tunica propria, which extends to the periosteum.[9] The tunica propria is often mesenchymal in appearance and consists of a loose network of fibrillar strands and relatively few connective tissue cells. Inconspicuous lymph vessels, moderate numbers of blood vessels and a few mucous and serous glands, as well as scattered large mononuclear cells and lymphocytes, are seen in this layer. The scattered masses of lymphoid tissue found in the tunica propria of the adult are not encountered in the infant. The histologic appearance of the middle ears is essentially the same as that of the sinuses (fig. 1 *C* and fig. 2 *C*).

Normally the lumens of the sinuses and ears are empty or contain an amorphous pink-staining precipitate, in which may be scattered cornified epithelial cells and other amniotic elements (fig. 3). Blood elements may be intermingled, particularly if the infant has inspired such substances during delivery. Occasional scattered leukocytes, both lymphocytes and polymorphonuclear granulocytes, may be present and are not considered significant unless they are present in relatively large numbers.

9. Schaeffer, J. P.: The Nose, Paranasal Sinuses, Naso-Lacrimal Passageways and Olfactory Organ in Man, Philadelphia, P. Blakiston's Son & Co., 1920. Rutledge, E. K.: The Paranasal Sinuses in the Newborn, Development and Pathology, Thesis, University of Colorado School of Medicine, 1933.

The frequent finding of foci of hemopoiesis in the tunica propria may cause confusion, but with a little experience one learns to identify these foci.

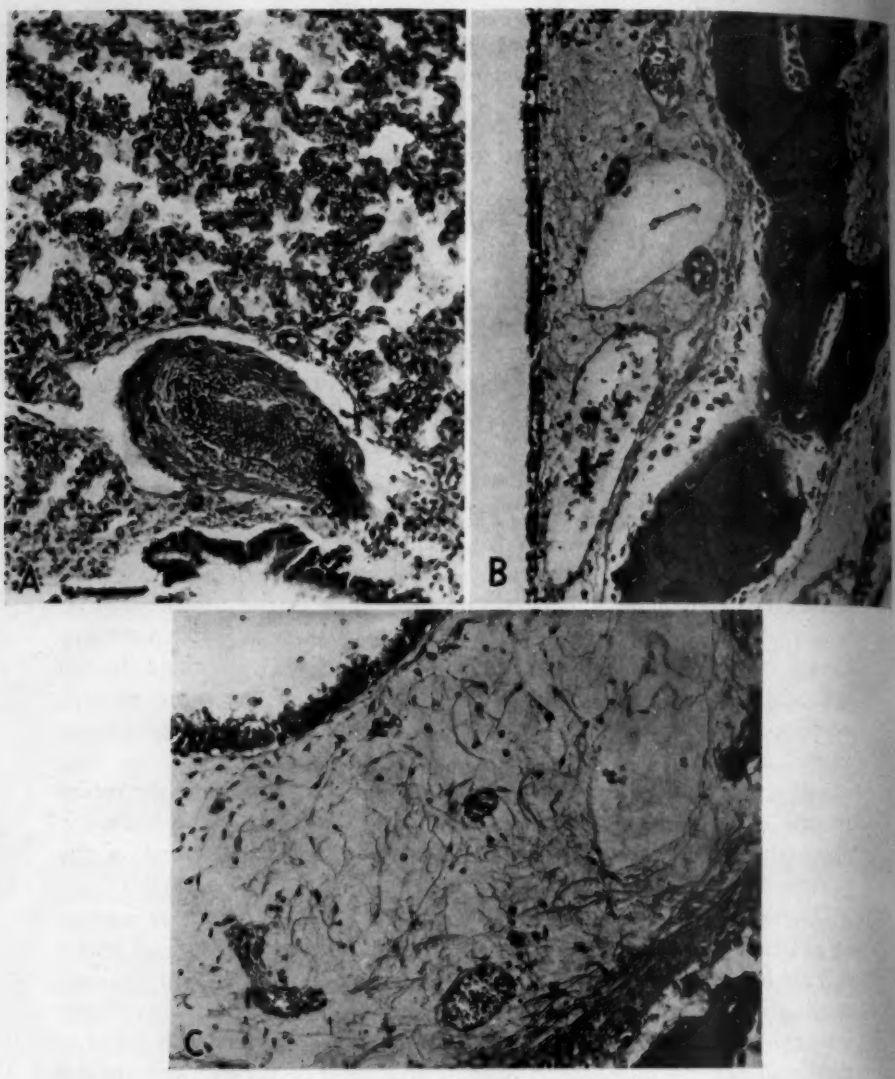

Fig. 1.—Photomicrographs (× 215) of histologic sections: *A*, poorly expanded lung of a liveborn infant. There is no evidence of inflammation or of aspiration of a significant amount of amniotic fluid. *B*, section of "normal" mucosa of the nasal sinus of the liveborn infant. *C*, section through "normal" mucosa of the middle ear of a stillborn infant.

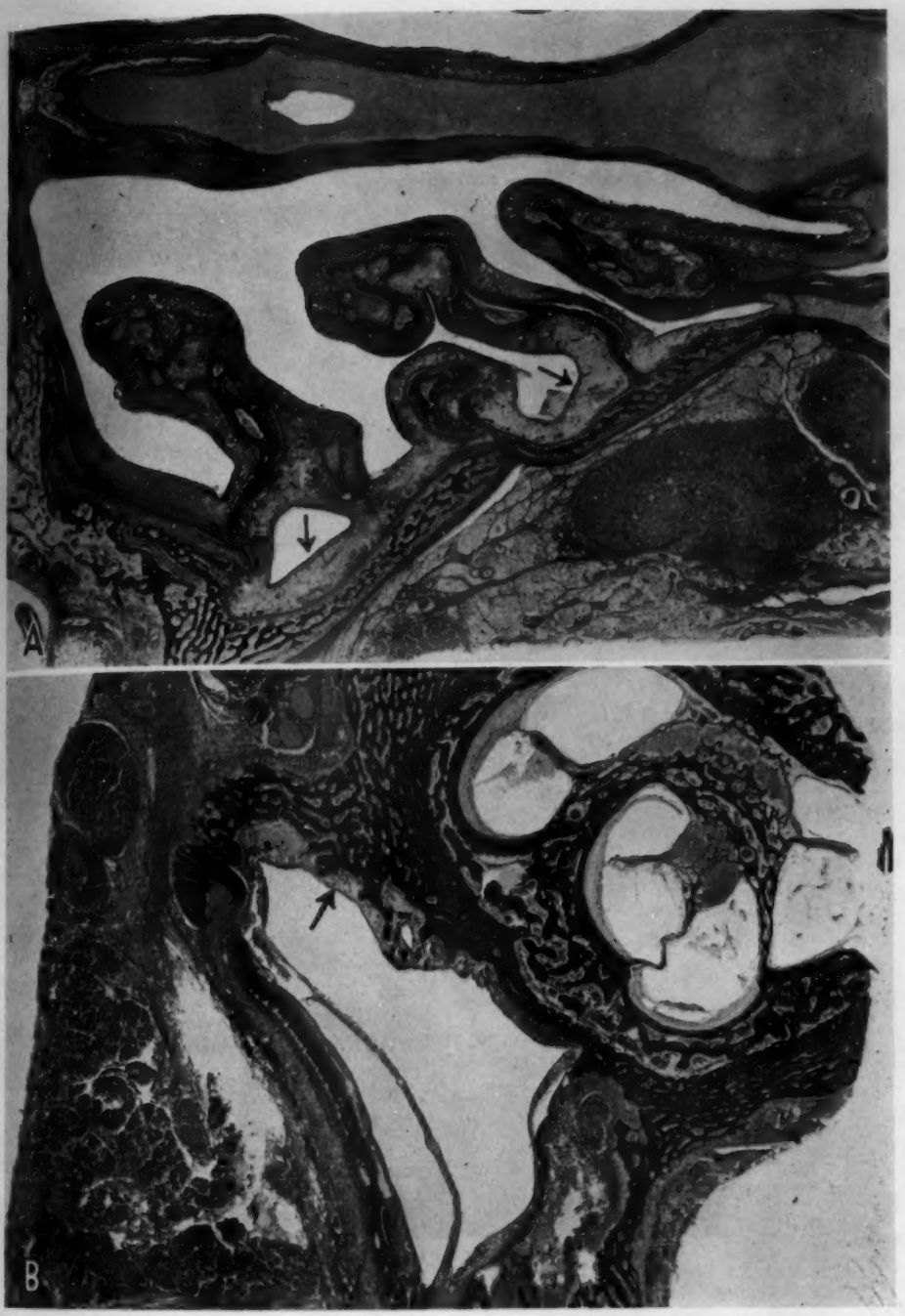

Fig. 2.—*A*, photomicrograph (× 9) of a histologic section through the nasal cavity of a liveborn infant. Arrows indicate typical mucosa of the nasal sinus. *B*, photomicrograph (× 9) of a histologic section through the middle and inner ear of a stillborn infant. An arrow is placed in the middle ear cavity and is directed toward the mucosa.

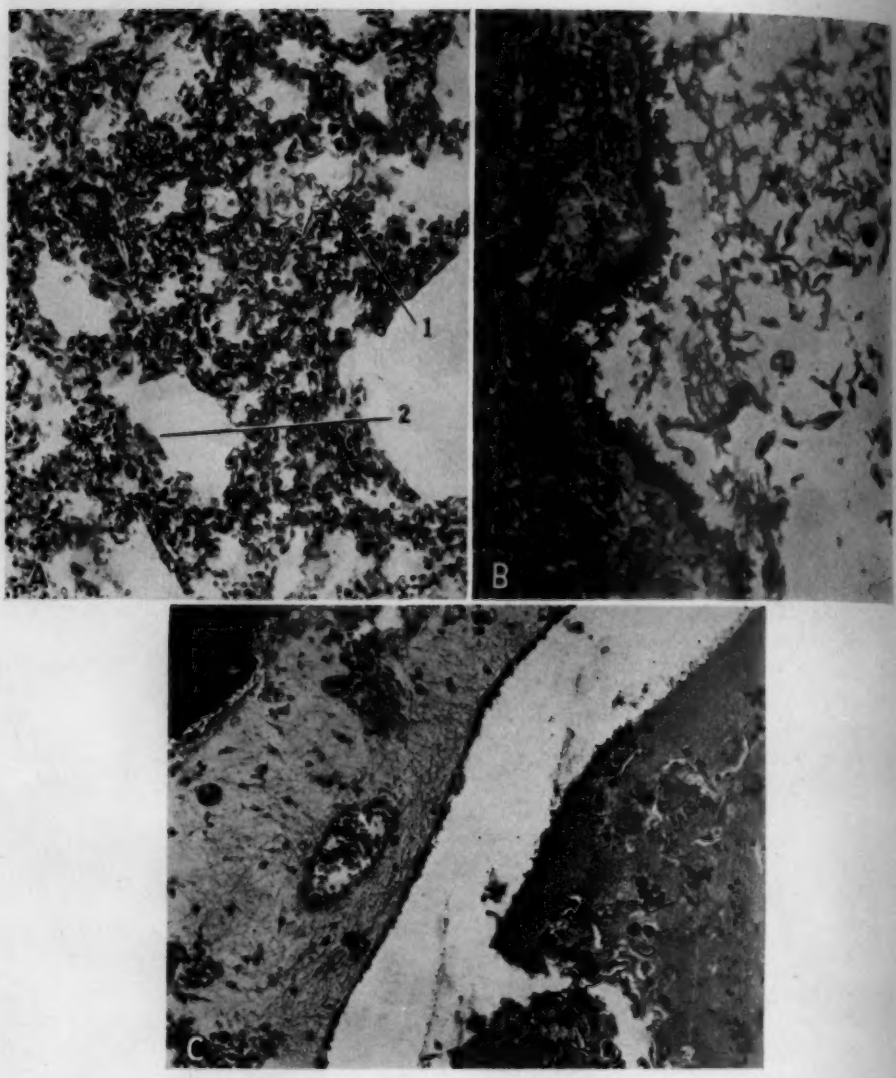

Fig. 3.—Photomicrographs (× 214) of histologic sections: *A*, section of lung of a liveborn infant showing cornified epithelial cells and vernix caseosa in the alveoli. *1* indicates epithelial cells; *2*, vernix caseosa. *B*, section through the nasal sinus of a liveborn infant showing amniotic elements in the lumen. *C*, section through the middle ear of a stillborn infant showing amniotic elements, a few scattered leukocytes and red blood cells in the cavity.

HISTOLOGIC DESCRIPTION OF LUNGS, SINUSES AND EARS OF NEWBORN IN WHICH INFLAMMATION IS PRESENT

Inflammatory changes in the lungs, ears and sinuses of the newborn cannot be recognized on gross examination alone in most instances. Hook and Katz [10] emphasized this point in regard to the diagnosis of pneumonia in stillborn and liveborn infants, and it is obvious that varying degrees of atelectasis, congestion and aspiration of amniotic fluid may simulate the appearance of true pneumonia. Gross examination of the middle ears and sinuses is almost equally unrevealing, as there is normally a gelatinous material present which may resemble thin pus and which may contain amniotic elements in varying amounts.

Accurate diagnoses can, however, be made on microscopic examination of the tissues. Congenital pneumonia shows some special features which differentiate it from the usual types of bronchial and lobar pneumonia. The inflammation is usually diffuse and fairly uniform throughout the entire lung, and the exudate consists of variable numbers of polymorphonuclear leukocytes, a few mononuclear cells, a variable number of red blood cells and amniotic debris. As Johnson and Meyer [3] stated, the diffuseness is probably due to the fact that the process commences in an atelectatic lung through which infection is widely spread by aspiration of contaminated fluid. Microscopic examination of the ears and sinuses in cases of inflammation shows the lumens to be occupied by variable amounts of exudate, made up of polymorphonuclear leukocytes, lymphocytes, monocytes and material from the amniotic cavity. The epithelial lining of the lumens is seldom disrupted, and the tunicae propriae are edematous, contain congested vessels and are infiltrated with leukocytes. In tables 1 and 2 I have indicated the findings in the 26 cases in which inflammation was demonstrated in the regions studied. Figure 4 illustrates the conditions as commonly seen.

OBSERVATIONS

Seventy cases have been studied. Thirty-one of the infants were stillborn. Thirty-nine infants were born alive. Nineteen were fetuses of about six or seven months' gestation, and the remainder approached term. In the entire group 44 were considered "normal" (23 stillborn and 21 liveborn). Those designated as "normal" showed considerable variation; some had absolutely clear lungs, ears and sinuses, whereas others showed amniotic debris, free blood and, occasionally, small numbers of leukocytes in the lumens and mucosa. When leukocytes were few and irregular in distribution, associated with hemorrhage or with plentiful amniotic debris and restricted to the lumens, I felt that they could not be considered as

10. Hook, H., and Katz, K.: Virchows Arch. f. path. Anat. **267**:571, 1928.

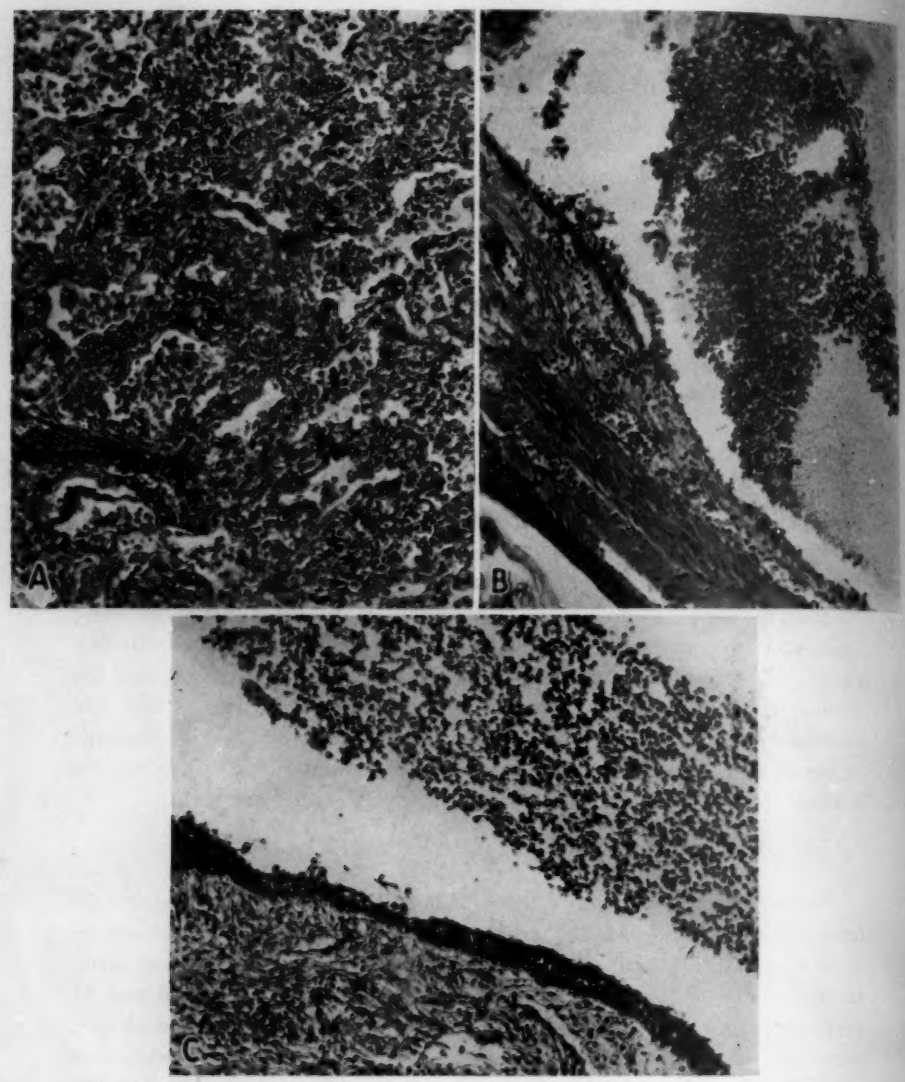

Fig. 4.—Photomicrographs (× 214) of histologic sections: *A*, section of lung of a liveborn infant showing well developed pneumonia. *B*, section of a nasal sinus showing inflammation. Purulent exudate and amniotic debris are present in the cavity. Congestion and slight leukocytic infiltration are seen in the mucosa. *C*, section from the middle ear of a stillborn infant showing inflammation. There is purulent exudate in the cavity as well as leukocytic infiltration of the mucosa.

positive evidence of inflammation. The presence of bacteria would be important if organisms could have been demonstrated ante mortem, but in this group of cases I found bacteria where there was no evidence of parenteral inflammation and noted great unevenness of distribution of these bacteria in all cases. These findings and the possibility of post-mortem contamination force me to disregard bacterial studies in this material. Figures 1, 2 and 3 illustrate the limits of "normal" variation in histologic appearance adopted for this study, and in all of the 44 cases which are reported as "normal" the conditions fall between these limits.

Case 1.—The subject was a premature fetus. The lungs were atelectatic, and little or no purulent fluid had penetrated into the alveoli, but scattered polymorphonuclears were seen in the bronchi. Purulent exudate and mucosal infiltra-

Table 1.—*Stillborn Infants*

No.	Length, Cm.	Sex	Inflammation in			Bacteria	Associated Pathologic Condition
			Lungs	Sinuses	Ears		
1	32	M	+	+	+	Few gram-positive cocci	
2	33	F	+	+	+	Mixed bacteria	Leukocytes in stomach
3	40	F	++	+	++	Few gram-positive cocci in ear	
4	42	M	0	++	+	Gram-positive cocci	Pulmonary atelectasis
5	43	M	±	++	+	None	Hemorrhagic condition of lungs
6	44	F	+++	+++	+++	None	Anomaly of the heart
7	46	M	±	++	++	None	Hemorrhagic condition of lungs; cerebral hemorrhage
8	52	F	++	+	++	Mixed, in lung only	Cerebral hemorrhage

+ indicates evidence of inflammation.

tion by leukocytes were seen in the sinuses and ears, indicating inflammation in the upper respiratory tract. This combination of findings suggests that infected material was present and in all probability would have penetrated into the alveoli of the lungs if the infant had lived to breathe.

Case 2.—The conditions seen in the premature infant in this case were similar to those in case 1.

Case 3.—The lungs, ears and sinuses all showed purulent exudate in the cavities and leukocytic infiltration in the surrounding tissues.

Case 4.—The sections of the sinuses showed leukocyte infiltration of the mucosa and purulent exudate in the cavities. The sections of the ear were poor, and the cavity had been opened previously, so that little exudate was seen, but the mucosa showed infiltration by leukocytes. The lungs were atelectatic and showed no evidence of inflammation. This case was the second of inflammation of the upper respiratory tract with complete atelectasis, which had prevented involvement of the lungs.

CASE 5.—The lungs were atelectatic, though less so than in the previous case since amniotic debris and a few scattered polymorphonuclears were seen in the alveoli. The vessels were much congested with blood, and free blood was present in the alveoli. The lungs were not definitely pneumonic, but in view of the fact that there was a well developed inflammatory reaction in both ears and sinuses the probable course of events was an infection of the upper respiratory tract which spread slowly to the lungs. I believe that at the time of death the lungs were in the congestive and hemorrhagic phase of inflammation whereas the upper respiratory system was more seriously involved. The association of conditions made possible the diagnosis of pneumonia.

CASE 6.—The lungs, sinuses and ears showed advanced inflammation, indicating that the causative agent had been acting for a considerable time before death. The parallelism of the reaction in all portions indicated that an infective agent had reached the lungs early, perhaps as the result of some degree of asphyxia and respiratory stimulation.

CASE 7.—This case is entirely similar to case 5. The cerebral hemorrhage doubtless occurred later than the infection and resulted from the efforts of the obstetrician to deliver a baby that was in poor condition. The hemorrhage may have been the immediate cause of death, but if the infant had been born alive, pneumonia would have caused almost immediate asphyxia and death.

CASE 8.—In this case, also, there was inflammation in lungs, ears and sinuses, although it was less advanced than in the previous case. Death had probably been due to cerebral hemorrhage, as the infection was in an early stage.

CASE 9.—The infant was premature and lived only a few minutes; therefore pathologic changes must have occurred prior to birth. The lungs were almost completely atelectatic, but scattered accumulations of polymorphonuclears were found in some bronchi and alveoli. This suggests that the leukocytes were probably inspired at about the time of birth and that there was not time for pneumonia to develop. The sinuses showed small amounts of exudate, but there was a larger amount present in the nasal cavity. This may have been for either of two reasons: (1) The material inspired may have been purulent amniotic fluid which did not reach the sinuses, or (2) respiration may have cleared the sinuses of purulent exudate which had been previously accumulated. A slight degree of mucosal infiltration around the sinuses suggests that both reasons must be considered. The ears showed a heavy exudate in the cavities and also advanced involvement of the mucosa and tunica propria, which proves that the otitis media was of fairly long standing. In summary, I believe that the amniotic fluid was infected a day or so before birth, caused inflammation in the ears and sinuses and reached the lungs at about the time of the first inspirations. Small, poorly developed sinuses may have retained little infected material, and this may account for the less advanced inflammatory reaction which was observed.

CASE 10.—The infant was slightly premature and lived only a few minutes. At death there was well developed, though somewhat irregularly distributed, pneumonia. The exudate in the lungs was seen both in conjunction with and separate from amniotic debris, though the latter was distributed fairly diffusely throughout the air spaces. The ears and sinuses showed a heavy purulent exudate and a mild degree of mucosal infiltration. The infiltration was less extensive than in case 9, suggesting that the amniotic fluid was purulent before aspiration. The bacterial studies were inconclusive.

CASE 11.—The infant lived three hours. There was well developed pneumonia as well as a considerable amount of amniotic debris in the lungs. The sinuses and ears contained rather small amounts of purulent exudate, but their mucosa was definitely infiltrated with leukocytes. It seems probable that this was a case of true infection, though the results of bacterial studies were not definite, and the

TABLE 2.—*Infants Born Alive*

No.	Age	Length, Cm.	Sex	Inflammation in: Lungs	Sinuses	Ears	Bacteria	Associated Pathologic Condition
9	10 min.	29½	M	±	+	++	Gram-positive cocci and rods in ear; gram-positive cocci in sinus	Slight jaundice
10	Few minutes	42	M	+++	+	+++	Mixed	
11	3 hr.	46	F	++	+	++	None	Cerebral hemorrhage
12	6 hr.	47	M	++	++	+++	Large gram-negative rods in sinus; small gram-positive rods in ear	Cerebral hemorrhage
13	7 hr.	30	M	+	+	++	None	
14	8 hr.	38	F	±	+	++	None	Vernix membrane in lungs
15	? hr.	43	M	+	±	+++	Gram-positive cocci in ear	Vernix membrane in lungs
16	? hr.	35	F	+	++	++	None	Abodminal hemorrhage
17	? hr.	35	M	±	+	++	None	Cerebral hemorrhage
18	16 hr.	37	M	+	++	±	Gram-positive cocci in ear	Sections of ear poor
19	17 hr.	32	M	+	+	+	Mixed (few)	
20	22 hr.	55	F	+	±	+	None	Hyperinsulinism
21	24 hr.	48	M	++	+	+	Mixed	Much amniotic debris in all regions; largyngitis
22	24 hr.	34	F	+++	+++	+++	Many gram-positive cocci	Cerebral hemorrhage
23	24 hr.	47	M	+++	++	+	Gram-positive cocci in lungs and sinuses	Vernix in lungs
24	26 hr.	47	F	+	++	+	Few gram-positive cocci	Cerebral hemorrhage; probable infection at birth
25	30 hr.	50	F	±	+	+	None	Cerebral hemorrhage, slight; probable postnatal infection
26	48 hr.	50	M	+++	+++	+++	Gram-positive cocci in sinuses	Cerebral hemorrhage; laryngitis; icterus

± indicates questionable, or borderline, inflammation.
+ indicates evidence of inflammation.

infection may have occurred at, or shortly before, birth. The cerebral hemorrhage was doubtless the direct cause of death, though the respiratory inflammation was certainly contributory.

CASE 12.—The appearance of the tissues was somewhat difficult to interpret. There was a massive exudate in the ears and a moderate exudate in the sinuses; the mucosa in both regions was only slightly infiltrated but was hemorrhagic. One cannot be sure whether the lumens contained inspired purulent fluid and the vascular congestion was secondary to cerebral hemorrhage, or whether the exudate

and congestion were manifestations of inflammation. The most probable explanation is that purulent fluid entered the ear and sinus cavities and brought about an inflammatory reaction. The lungs contained considerable amniotic fluid as well as leukocytes. Bacterial studies showed a few scattered bacteria of different kinds.

Case 13.—A 5½ month fetus showed evidence of early inflammation in all parts of the respiratory tract. If infection occurred at birth, the inflammation may have developed in the seven hours that the infant lived.

Case 14.—A 7 month fetus lived eight hours and showed conditions similar to those in case 13. The exudate was scanty in all parts, but the infiltration of the mucosa of the sinuses and ears and of the alveolar walls was definite, suggesting a developing inflammation rather than aspiration of purulent fluid. The prematurity and the vernix membrane in the lungs were probably more significant in causing death than was the degree of infection present.

Case 15.—The exact duration of life of the infant could not be discovered, as he was born at home; it was estimated as about twelve hours. The lungs showed a spotty distribution of pneumonia, the sinuses a small amount of exudate, and the ears marked inflammation. The aural cavities contained a thin fibrinopurulent exudate, and the mucosa showed marked infiltration by leukocytes, as well as dilatation and congestion of the vessels. Amniotic debris and pneumonic exudate in the lungs were believed to be the cause of asphyxia and death.

Case 16.—The exact duration of life is not known. My estimate, however, is two to three hours or less. There were an acute inflammatory reaction in the ears and sinuses and early pneumonia in the partially atelectatic lungs. This is suggestive of an infection carried by the amniotic fluid and acting for some time in the upper respiratory tract and later affecting the lung tissue. The abdominal hemorrhage was doubtless the result of vigorous efforts to stimulate an infant in poor condition.

Case 17.—The subject was a 5½ month fetus. Again the duration of life is not known. I estimate that he lived less than three hours. The lungs were atelectatic and contained amniotic debris and scattered polymorphonuclear leukocytes. The sinuses contained a moderate amount of debris, in which leukocytes were scattered. It is, however, of importance that the nasal cavity contained a purulent exudate and that in places there was heavy infiltration of the mucosa with necrosis. The ears showed a small amount of exudate and an acute inflammatory infiltration of the mucosa. Cerebral hemorrhage was doubtless the immediate cause of death.

Case 18.—A premature infant lived sixteen hours and showed an early inflammation in the lungs, ears and sinuses. The length of life and the evident age of the infectious process suggest that bacteria were introduced at or after birth. The gram-positive cocci seen in the sinuses and ears were probably significant, as they were diffusely scattered and present in considerable numbers. The fact that all regions studied showed the infectious process speaks for inoculation at birth rather than later.

Case 19.—A premature infant lived seventeen hours and showed evidence of an early inflammation in all portions of the respiratory tract. As in case 18 the age of the newborn and the progress of the inflammatory process suggest infection at or after birth, and the parallelism of conditions in all parts makes infection at birth seem more likely than a later introduction of organisms.

CASE 20.—The infant was born of a diabetic mother. The immediate cause of death was hyperinsulinism, with hypertrophy and hyperplasia of the islands of Langerhans. The lungs showed that there had been extensive aspiration of amniotic fluid; polymorphonuclears were scattered among cornified epithelial cells and vernix. The sinuses and ears showed a heavy purulent exudate. Therefore, it is evident that aspiration of infected material complicated the endocrine condition.

CASE 21.—Inflammatory reactions were seen in the lungs, ears and sinuses. The lungs were most seriously involved, and there was also an acute inflammation of the larynx. It is possible that intratracheal methods of resuscitation were used, and the laryngitis initiated, after which infection spread to the lungs and upper respiratory tract.

CASE 22.—A premature infant showed advanced inflammation in the lungs, ears and sinuses. In all regions the inflammation was equally advanced, and its duration must have been longer than the extrauterine life of the infant. Cerebral hemorrhage was noted and doubtless contributed considerably to death, but the severe infection must be considered as also contributory.

CASE 23.—A day old infant showed inflammation in the lungs, ears and sinuses. The lungs were most severely affected and the ears least. The pneumonia was sufficiently advanced to indicate an antenatal infection.

CASE 24.—A cerebral hemorrhage was of prime importance, and a minor degree of respiratory inflammation was more or less incidental, as the inflammation was in an early stage in all regions investigated. The lungs suggested aspiration of food material, and this may have been the etiologic factor.

CASE 25.—This case is entirely similar to case 24.

CASE 26.—In a 2 day old infant there was advanced inflammation in the lungs, ears and sinuses, as well as laryngitis. The degree of involvement led to the assumption that an antenatal infection was the etiologic factor. Tentorial lacerations were also present, but there was little free blood in the cranial cavity, and therefore I believe the respiratory infection to have been the chief cause of death.

COMMENT

Of the 31 stillborn infants examined, 16 were markedly premature, varying between 27 and 47 cm. in length. Seven of the 8 infants showing inflammation of the respiratory tract were premature, and in this group the incidence of cerebral hemorrhage was low, whereas in infants approaching term respiratory inflammation occurred only once and cerebral hemorrhage was a frequent finding. Of the 39 infants born alive, 30 were less than 1 day old, and, of these, 12 showed pathologic changes in the respiratory tract. Of the remaining 9 infants, 1 day or more of age, 6 showed involvement of the lungs, ears and sinuses; 3 of these 6 showed sufficiently advanced lesions to establish a diagnosis of antenatal disease, and the remaining 3 may have been infected at or after birth. Cerebral hemorrhage was seen frequently, and in cases in which both hemorrhage and pneumonia were noted it is easy to understand how an

injury at birth would lead to asphyxia with aspiration of material from the uterus or the birth canal, and also how asphyxia would predispose to cerebral hemorrhage of the nontraumatic type. Thirty-seven per cent of the entire number of fetuses and infants had inflammatory changes in the respiratory system; 26 per cent of the stillborn infants and 46 per cent of the liveborn infants showed inflammation. Thus it is evident that inflammation of the respiratory system, whether due to infection or to other causes, is definitely to be reckoned with in preventing deaths of newborn infants.

The nature of intrauterine existence and the finding of evidence of inflammation in stillborn or recently liveborn infants in, and limited to, the regions penetrated by amniotic fluid make me believe that aspiration of infected material is the method of inoculation of infective organisms into the respiratory system and that amniotic fluid must be the carrier of the infectious or irritative agents. Kaldor [11] called attention to the fact that exudate is often present in the bronchi, and this is further evidence for the aspiration theory. The finding of advanced inflammatory changes in sinuses and ears in association with uninfected atelectatic or hemorrhagic lungs (3 cases) is interesting evidence that the glottis may be closed during intrauterine life and that amniotic fluid may not penetrate into the lungs under certain conditions. When the lungs show expansion and show inflammation paralleling that in the sinuses and ears, I feel justified in assuming that toxemia of the infant or some other factor brought about a degree of asphyxia which induced respiratory effort. The fact that 7 of the 8 subjects showing inflammation were markedly premature suggests that toxicity, possibly bacterial, was acute enough to cause premature delivery of the fetus.

Aerogenous infection after birth must be considered as possible in those cases in which infants lived for some time and showed inflammatory reactions which appeared recent enough to justify such a diagnosis. Metastatic modes of infection must be discarded in the explanation of the conditions found in this series, as none of the infants showed inflammation in any other organ. Inoculation by way of the placental circulation cannot be considered as a possibility except in rare instances, because of the specificity of the location of the infections; with infection of the blood stream there should be involvement of a number of organs in any series as large as that presented.

The placenta and membranes were examined in about half of the cases in the entire series, and in 16 of the 26 cases in which the respiratory tract showed inflammation. In this group of 16 cases there were 4 in which the placenta and membranes showed considerable purulent inflammatory reaction and 5 in which they showed moderate focal

11. Kaldor, J.: Am. J. Obst. & Gynec. **25**:113, 1933.

inflammation; in 7 these tissues were entirely normal. It is thus seen that in the majority of cases in which there was evidence of aspiration of infected amniotic fluid there were also inflammatory changes in the amniotic sac. I agree with Johnson and Meyer [3] that the time when infection reaches the lungs is variable but that infection probably reaches the upper respiratory tract very soon after contamination of the amniotic fluid. In cases in which the membranes rupture a considerable time before delivery, infection may be introduced from the lower part of the birth canal and into the amniotic sac at that time or soon after. When the membranes rupture at the time of delivery, the mode of entry of bacteria into the amniotic sac is less clear. Johnson and Meyer [3] expressed the opinion that the entrance of infection might be through the intact membranes or through slight premature ruptures which escape notice. They reported 2 cases in which the membranes ruptured just before delivery, and yet the placentas and membranes were acutely inflamed. In the present series I have incomplete information concerning the progress of delivery and therefore cannot form an opinion.

The study of sections of lungs, ears and sinuses stained by Gram's method has given most unsatisfactory results, as organisms have been found in cases in which no exudate or leukocytic infiltration was noted, while, on the other hand, no organisms or a scanty number of mixed varieties have been found when there was an extensive inflammatory reaction. I therefore cannot state definitely that inflammation in any of the regions studied is invariably due to infection, but I reiterate that leukocytic infiltration and purulent exudate are so interpreted in older persons. It is generally accepted that a foreign body reaction has certain morphologic characteristics which differentiate it from infection, i. e., monocytic infiltration, phagocytic activity and presence of foreign body giant cells. In 2 cases in this group in which the observations are reported as within the "normal" range, large foamy monocytes were encountered, some of which were multinucleated and were considered to be of the foreign body type; in all other cases the reactions were typical of pyogenic infection.

The observation that leukocytic infiltration and purulent exudate are frequently seen in greater quantities in the middle ears than in the lungs or the sinuses indicates to me that the ear is a better index of infection than the other two regions. The reason for such a finding is that infected material reaches the middle ear easily through a wide horizontal eustachian tube [12] and remains localized in a cul-de-sac. The sinuses are also a good index, but the ostiums are small, so that infected material may reach the sinuses in lesser amounts. Both ears and sinuses are subject to the effects of suction once respiration is established, and an

12. Asherson, N.: Arch. Dis. Childhood **7**:159, 1932.

exudate may be drawn out, leaving only mucosal infiltration to reveal the presence of infection. The lung retains infected material once this has reached the alveoli, but, as is illustrated in a few cases, the alveoli may remain atelectatic and uninfected long after the upper respiratory system has been invaded.

As can be seen throughout the cases studied, there is a parallelism between the inflammatory reactions in the ears, sinuses and lungs. This reenforces the belief that the mode and means of infection are the same for all three locations and that amniotic fluid is the probable carrier of the infective agent.

SUMMARY

The problem of infection of the respiratory system in the newborn, whether stillborn or liveborn, is discussed in regard to the mode of involvement and the etiologic factors. The means of recognition of amniotic fluid are discussed. In a series of 70 cases the middle ears, sinuses and lungs have been examined, and the findings have been tabulated and discussed.

Inflammatory reactions were noted in 37 per cent of the total number of fetuses and infants examined, in 26 per cent of the stillborn infants and in 46 per cent of the infants born alive (all under 2 days of age at death).

Aspiration of infected amniotic fluid is believed to be the cause of the pathologic picture presented. It is suggested that infection of the fluid may occur after early rupture of the membranes even though the ruptures were so slight as to escape notice.

Study of sections treated with Gram's stain has given such variable findings that this method is considered unreliable for ascertaining the presence or absence of infection. A careful microscopic study of the structures involved represents the only reliable method of determining the presence or absence of an infectious process.

The most significant observation in this study was the apparent parallelism between the inflammatory conditions seen in the ears, sinuses and lungs, indicating a common source of infection.

ULCEROGLANDULAR TULAREMIA

REPORT OF THREE FATAL CASES WITH AUTOPSIES

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The fatality rate of tularemia is reported as 5.6 per cent by the United States Public Health Service, 6.0 per cent. by Foshay [1] and 11 per cent by Simpson.[2] Of 23 persons in Cleveland who had tularemia during the winter of 1937-1938, 3 died. The autopsies on these 3 persons are included in the present report.

Studies of the autopsy material in 57 cases have been published by Lillie and Francis,[3] Foshay,[1] Pund and Hatcher,[4] Matthews,[5] Weilbaecher and Moss,[6] Allen and Smith [7] and by Kimmelstiel and Caldwell.[8]

REPORT ON THREE ADDITIONAL CASES

CASE 1.—J. C., a white man aged 45, admitted to City Hospital on Nov. 20, 1938, had hunted and cleaned rabbits without wearing gloves on November 15 and 16. November 18 a severe generalized throbbing headache developed, followed by a slight chill lasting for a few minutes, generalized muscular pain and fever. There was soreness about the finger nails of both index fingers, which he had trimmed closely before going hunting.

The temperature on admission was 39 C. (102.2 F.), the pulse rate 116, the respirations 24 per minute and the blood pressure 120 systolic and 60 diastolic. The sensorium was slightly clouded. The abdomen was soft and the liver and spleen not palpable. There were small superficial ulcers about the sides of the nails of both index fingers, which were clean but surrounded by a definite zone of redness, beyond which the tissues for a few millimeters appeared dusky and

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1. Foshay, L.: Arch. Int. Med. **60**:22, 1937.
2. Simpson, W. M.: Arch. Path. **6**:553, 1928.
3. Lillie, R. D., and Francis, E.: The Pathology of Tularemia in Man, National Institute of Health Bulletin 167, United States Treasury Department, Public Health Service, 1937.
4. Pund, E. R., and Hatcher, M. B.: Ann. Int. Med. **10**:1390, 1937.
5. Matthews, W. R.: New Orleans M. & S. J. **90**:479, 1938.
6. Weilbaecher, J. O., Jr., and Moss, E. S.: J. Lab. & Clin. Med. **24**:34, 1938.
7. Allen, H. C., and Smith, M. G.: Arch. Path. **26**:1052, 1938.
8. Kimmelstiel, P., and Caldwell, H. W.: Am. J. Path. **15**:127, 1939.

cyanotic. They were much more tender than their appearance warranted. There was no lymphangitis, but one large soft tender lymph node, measuring about 3 cm. in its greatest diameter, was felt in the left axilla. The rest of the physical examination gave negative results.

On the day after admission administration of sulfanilamide was begun. An initial dose of 40 grains (2.6 Gm.) with an equal dose of sodium bicarbonate was given orally and thereafter 20 grains (1.3 Gm.) every four hours. The temperature remained high, and the patient became irrational. On November 23 and on the following day he was given 400 cc. of convalescent whole blood with an agglutination titer of 1:320. Stupor followed. On November 24, after having received a total of 380 grains (25.3 Gm.), the patient, unable at this time to swallow, was given 60 grains (4 Gm.) of sulfanilamide by hypodermoclysis. Coma ensued, and he died on November 24, four and one-half days (one hundred and six hours) after admission and six days (one hundred and forty-eight hours) after the onset of illness.

The urine was normal, as was the blood except for leukocytosis (white cell counts, 19,000 and 30,000, largely polymorphonuclears). The sulfanilamide level in the blood on the fourth day in the hospital was 13.2 mg. in 100 cc. Two hours before death the carbon dioxide–combining power of the blood was 23 volume per cent and the blood urea nitrogen was 40.0 mg. in 100 cc. The agglutination titer of the patient's serum against Pasteurella tularensis was 1:160 on the day of death, having been negative prior to this time. The final clinical diagnosis was: ulceroglandular tularemia and acidosis.

Autopsy.—The postmortem examination was started eleven hours after death. There was definite icterus of the skin and mucous membranes. There were small ulcers about the tips of the nails of both index fingers. The axillary lymph nodes were enlarged bilaterally, some of them measuring as much as 2.5 cm. in length. All nodes were very soft, and on section presented many areas of focal necrosis, which had almost obliterated the architecture.

The heart weighed 405 Gm. and was diffusely dilated but showed no other abnormality.

The lungs were voluminous. Throughout all lobes were small, roughly spherical gray nodules, few in number and varying from 1 to 3 mm. in diameter, not sharply circumscribed but blending into the surrounding tissue.

The bronchopulmonary, mediastinal, splenic, superior pancreatic and portal lymph nodes were enlarged and showed foci of necrosis similar to those described in the axillary nodes, although the involvement was less severe.

The liver weighed 2,000 Gm. and showed miliary nodules varying in diameter from 1 to 2 mm., both beneath the capsule and throughout the liver substance. These nodules were roughly spherical, pale yellowish gray, and of about the same consistency as the liver. In contradistinction to the typical miliary tubercle, they blended marginally with the surrounding tissue.

The spleen weighed 450 Gm. and was pultaceous. Beneath the capsule and in the parenchyma there were many small nodules similar to those in the liver but more numerous.

The remainder of the organs, including the brain, revealed no gross lesions.

Microscopic Observations.—The axillary lymph nodes were the seat of focal necrosis, which had almost destroyed some of them. The center of a focus was composed chiefly of fragmented cellular debris, while the marginal zone was composed of large mononuclears and macrophages in varying stages of degeneration. Foci were found predominantly in the peripheral sinuses but could be seen

in any portion of the node. Where the process had extended through the capsule, there was considerable periglandular necrosis as well as severe thrombophlebitis of periglandular vessels. The lesions in the portal superior pancreatic and splenic nodes were similar but less extensive.

The lungs were the seat of mild emphysema. The pulmonary lesions seen grossly were small nodules of alveolitis consisting of some fibrin and an exudate of large mononuclear cells with a moderate number of lymphocytes and red corpuscles and an occasional polymorphonuclear leukocyte and plasma cell (figs. 1 and 2). A striking feature was the phagocytosis by mononuclears, which contained nuclear fragments, red corpuscles and large vacuoles (fig. 2), only a few of which stained with scarlet red. The larger foci frequently showed frank necrosis of the center with only ghostlike remnants of the septums. Necrosis was absent in the small nodules.

Scattered throughout the liver were many foci similar to those seen in the lymph nodes. They varied in size from small groups of cells to lesions as large as an entire lobule and were not located in any uniform position in the lobule.

The sections of the spleen revealed marked hyperemia of the pulp and malpighian corpuscles, which were small. The architecture was greatly distorted by foci of coagulation necrosis, varying in size and located largely within the pulp, though often encroaching on lymphoid follicles. Rarely one lay entirely within a follicle. They were like those observed elsewhere, but there was no peripheral proliferative reaction.

The kidneys were the seat of severe tubular degeneration. No specific foci were seen. Sections of the heart, urinary bladder, prostate, testes, stomach, small and large intestine, pituitary, brain and bone marrow showed no specific or noteworthy lesions.

No organisms were demonstrable in bacterial stains of the axillary nodes or lungs. Cultures of the heart's blood post mortem in brain broth yielded no growth. However, organisms identified as Pasteurella tularensis by morphologic and cultural characteristics and by agglutination against specific antiserums were isolated from the right axillary node, spleen and liver.

Case 2.—A. H., a white man aged 49, admitted on Dec. 1, 1938, complaining of fever and general malaise, had dressed rabbits five days prior to admission without wearing gloves and despite a small abrasion on the index finger of the left hand. The following day he complained of fever and general malaise, which forced him to go to bed. On the day prior to admission he became delirious and vomited several times. He complained of chilliness and was perspiring profusely.

The patient's wife assisted him in dressing the rabbits. She, too, became ill with a relatively mild type of ulceroglandular tularemia and made an uneventful recovery.

On admission the patient was completely disoriented and seriously ill. The temperature was 41.2 C. (106 F.), the pulse rate 120, the respirations 38 per minute, and the blood pressure 100 systolic and 65 diastolic. There was a superficial ulcer, 3 mm. in diameter, on the dorsum of the left index finger, tender to palpation, with a border of redness, but not indurated (fig. 3). The left axillary nodes were enlarged and tender. The epitrochlear and other superficial nodes could not be felt. The heart and lungs were clinically normal. The liver and spleen were impalpable and remained so during the entire illness.

No examination of the urine was recorded. The blood showed moderate isochromic anemia and leukocytosis (white cell count 10,200, principally poly-

morphonuclears). A roentgenogram of the chest, taken with the patient recumbent, was interpreted as showing a nodular increase in density of the markings throughout both lung fields; there was no evidence of pneumonia. Agglutinations of Pasteurella tularensis were negative in dilutions of 1:40 to 1:640 on the first and second hospital days. On the latter date the blood urea nitrogen was 55.7 and creatinine was 3.3 mg. in 100 cc.

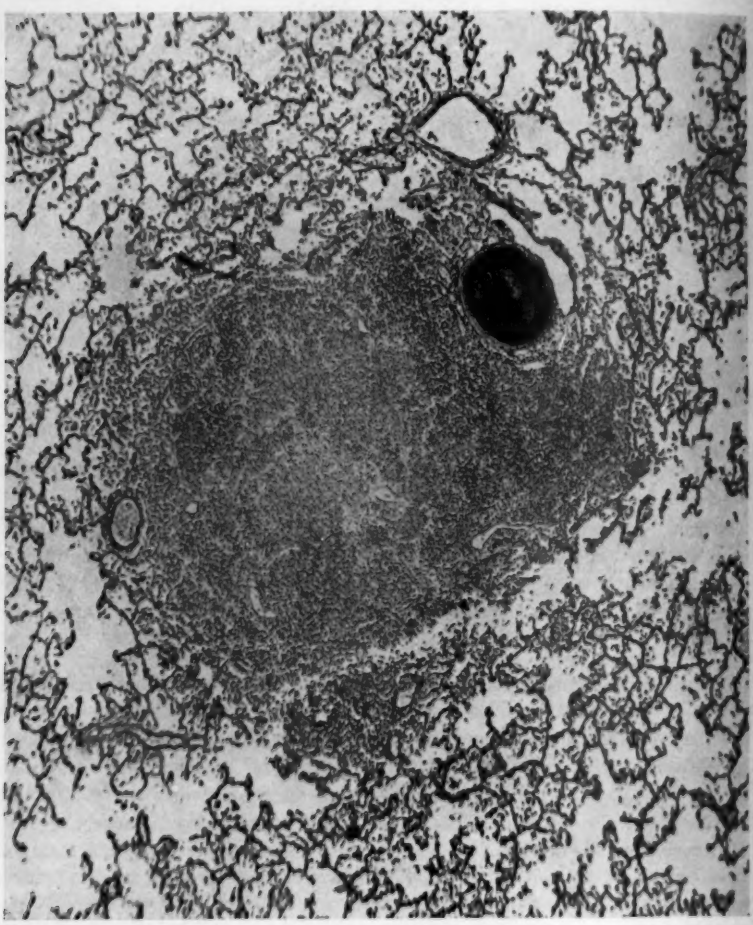

Fig. 1 (case 1).—Section of lung showing isolated focus with central necrosis; × 35.

After admission the patient was given antitularemic serum intravenously in doses of 15, 90, 60, 60 and 45 cc., a total of 270 cc. within thirty hours. Further treatment was symptomatic. His temperature remained above 40 C. (104 F.), and he became unconscious about forty-eight hours after admission. He died on December 3, fifty-nine hours after admission and six days after the onset of his illness. The final clinical diagnosis was: ulceroglandular tularemia.

Autopsy.—The postmortem examination was started eight and one-half hours after death. There was no icterus. The left axillary lymph nodes were moderately enlarged, soft and discrete and on section showed focal areas of necrosis, mostly

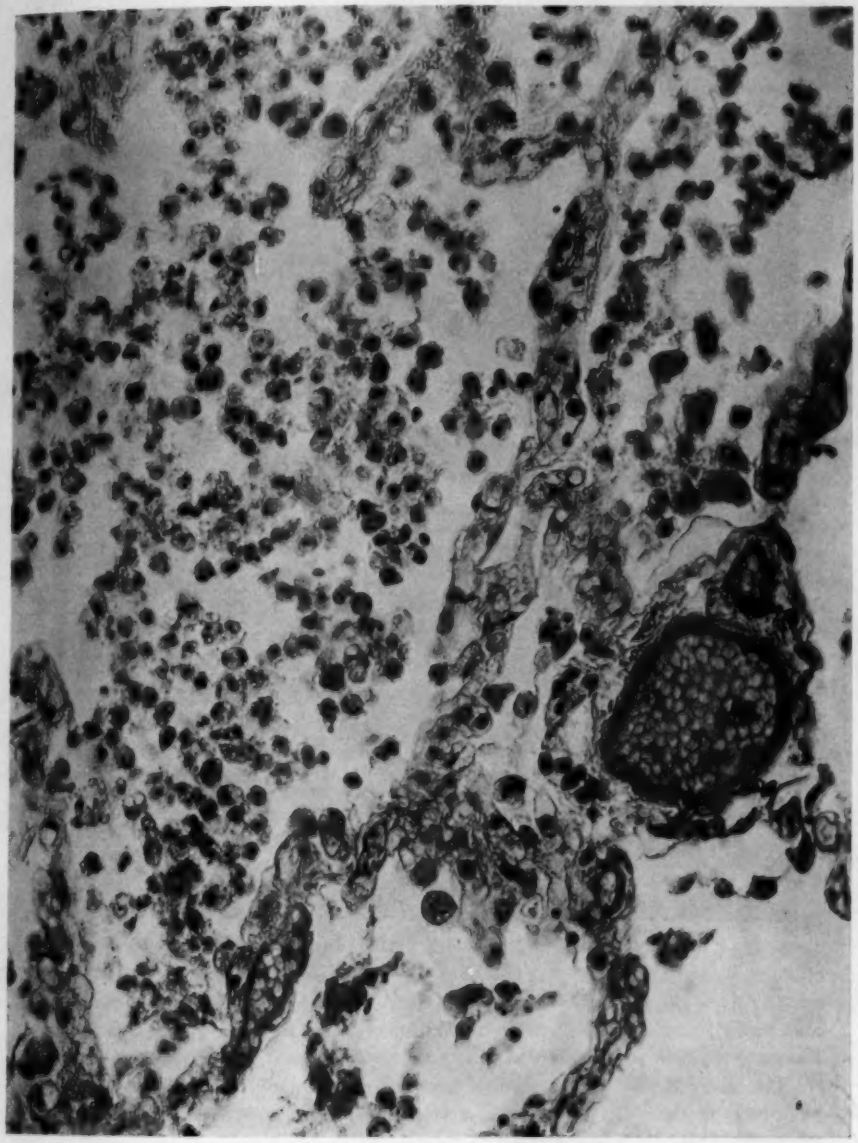

Fig. 2 (case 1).—Section of lung showing character of exudate; × 486.

in the peripheral portions of the nodes. None of the other superficial lymph nodes showed any abnormalities.

The posterior and dependent portions of the lower lobes of both lungs were consolidated. Small, pale yellowish pink nodules stood out on the surface in the areas of consolidation but not elsewhere. One large solitary nodule, 14 mm. in diameter but otherwise like the nodules described, was seen in the left lower lobe immediately beneath the pleural surface.

The bronchopulmonary, mediastinal, superior pancreatic and splenic lymph nodes were enlarged and soft and on section showed small, pale yellow foci which gave the nodes a distinctly mottled appearance.

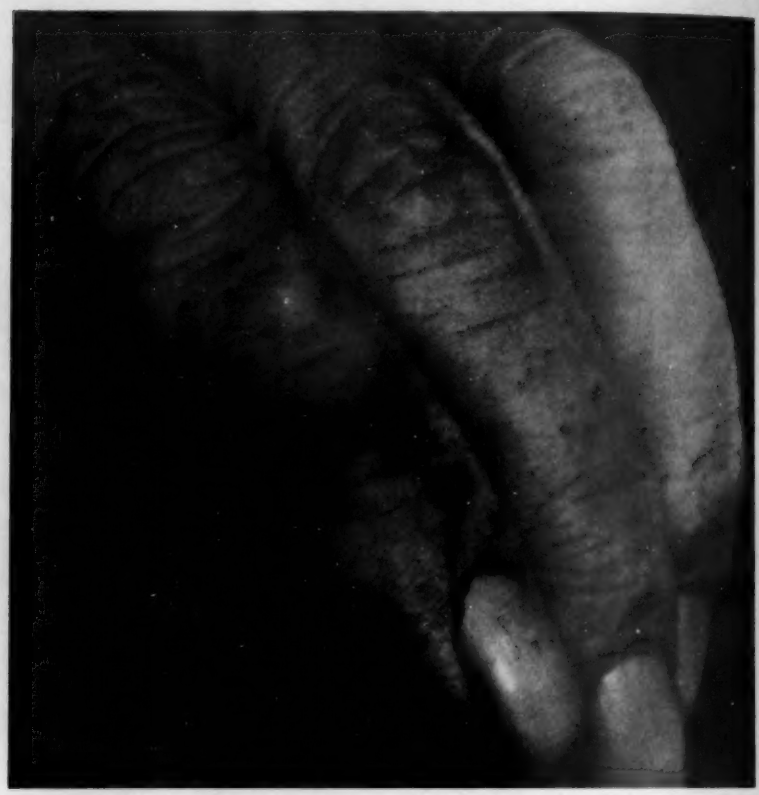

Fig. 3 (case 2).—Primary lesion on left index finger.

The liver weighed 1,725 Gm. and the spleen 260 Gm. Both organs were swollen and showed small nodules throughout, similar to those seen in case 1. No focal lesions were seen in the kidneys.

The stomach and small intestines were filled with dark blood. At a point 7 cm. proximal to the pylorus on the lesser curvature were several small superficial ulcers, one of which had a small blood clot adherent to it.

The vertebrae and the cranium and its contents showed no lesions.

Microscopic Observations.—Sections of the axillary, bronchopulmonary, mediastinal, superior pancreatic, portal and splenic lymph nodes revealed focal necrosis essentially the same as that described in case 1.

Aside from mild emphysema and passive hyperemia throughout, the lungs showed diffuse bronchopneumonia in the lower lobes similar to that in case 1. Necrosis was seen only in the large nodule of the lower lobe of the left lung and was almost coextensive with the lesion. The bronchi were the seat of mild nonspecific chronic inflammation. Bacterial stains revealed no organisms. The lesions in the liver and spleen were similar to those in case 1.

Section of the gastric ulcer revealed acute ulceration extending into the submucosa and covered with a partially organized blood clot. About the base of the clot the submucosa was infiltrated by large numbers of lymphocytes. There was one small focal area of lymphocytes, macrophages and a few large mononuclear and polymorphonuclear cells which appeared much the same as those seen in the liver and spleen but the focus did not show necrosis.

Sections of the rest of the organs showed no lesions suggestive of tularemia.

Organisms identified as Pasteurella tularensis by morphologic and serologic characteristics were grown on culture of material from the left axillary and mediastinal lymph nodes, liver and spleen. Postmortem culture of the heart's blood in brain broth showed no growth.

Case 3.—C. D., a white man aged 52, admitted on Dec. 31, 1938, began to have chills, fever, a productive cough and progressive malaise eight days prior to admission. It was only after he had been in the hospital for twelve hours that a history of a wound from puncture by a rabbit bone two days before admission was obtained.

On admission his temperature was 38.6 C. (101.5 F), the pulse rate 85, the respiratory rate 32 per minute and the blood pressure 180 systolic and 80 diastolic. He was having a chill at the time of examination and was slightly cyanotic and dehydrated. Many sibilant rales were present over the entire chest, while there were crepitant rales and bronchial breathing at the bases of the lungs. The liver and spleen were not palpable. A large puncture wound with undermined edges and a purulent discharge was present on the volar surface of the right index finger. The right axillary lymph nodes were enlarged, soft, discrete and very tender.

The urine had a specific gravity of 1.015, was acid and contained albumin (1 plus) with an occasional pus cell. The blood contained 5,000,000 red cells and 17,600 white cells per cubic millimeter; the hemoglobin was 15.6 Gm. (Sahli). A smear of pus from the ulcer showed a mixed flora; on culture Staphylococcus albus was recovered. Two blood specimens taken on January 1 gave no growth.

His temperature rose to 41 C. (105.8 F.) within twelve hours, and he became delirious. Agglutination of Pasteurella tularensis was positive up to a dilution of 1:320. He was given 250 cc. of whole blood and 30 cc. of antitularemic serum. An initial dose of 20 grains (1.3 Gm.) of sulfanilamide was given at 2 p. m. January 1 and thereafter 20 grains (1.3 Gm.) every four hours with equal amounts of sodium bicarbonate; he received a total dose of 120 grains (7.8 Gm.). There was no determination of the blood level of sulfanilamide. The temperature remained above 40 C. (104 F.). January 2 he became more delirious and later comatose. Shortly before death his temperature reached 42.2 C. (107.9 F.). He died January 3, fifty-five hours after admission and about ten days after the onset of his illness. The final clinical diagnosis was: ulceroglandular tularemia, bilateral bronchopneumonia and infected wound of the right index finger.

Autopsy.—The examination was started five hours after death. There were several areas of ecchymosis over the body. The right axillary lymph nodes were enlarged, soft and discrete. The largest node measured 3.5 cm. in length and on

section showed almost complete necrosis with hemorrhage. No hemorrhage was seen in any of the other nodes, but all were enlarged and on section showed pale yellow areas of focal necrosis, which in some instances were conglomerate and involved almost the entire node. The other superficial nodes were not enlarged. The lower halves of both rectus muscles were almost completely replaced by blood, which had ruptured through the posterior rectus sheath, extravasated into the preperitoneal space and extended down over the fundus of the urinary bladder and into both spermatic cords. There was no blood in the peritoneal cavity.

The heart weighed 460 Gm. and was diffusely dilated. The most dependent and posterior portions of the lower lobes of both lungs, approximately 20 to 30 per cent, were consolidated, and superimposed were many pale yellow and gray areas similar to those observed in the previous cases. The bronchopulmonary and mediastinal lymph nodes were enlarged and soft and on section showed many focal areas of necrosis.

The liver weighed 2,800 Gm.; the spleen, 650 Gm. They, too, showed many small foci of necrosis throughout. The splenic, superior pancreatic and portal lymph nodes were enlarged and on section showed small yellow foci of necrosis. There were several small areas of hemorrhage beneath the serosa of the stomach, which furthermore contained 200 cc. of blood-stained material. Many small ulcers paralleled the mucosal folds; some were superficial, while others extended down to the muscularis. Many were covered with small blood clots.

The other organs, as well as the cranium and its contents, showed no gross disease.

Microscopic Observations.—All lobes of the lungs showed small patchy areas of bronchopneumonia, which in the lower lobes were confluent. The exudate differed from previous ones in that there was a larger proportion of polymorphonuclears and a larger amount of fibrin in it. Many of the smaller bronchi were filled with exudate similar to that in the alveoli. The bronchopulmonary and mediastinal lymph nodes were the seat of severe focal necrotizing lymphadenitis.

The liver showed severe fatty metamorphosis and small focal accumulations of leukocytes with central necrosis. There was severe hyperemia of the splenic pulp with acute hyperplasia of the pulp cells. The architecture was greatly distorted by foci of necrosis, which were located chiefly but not solely in the hypoplastic lymph follicles and in some instances had completely destroyed them.

Sections of the right axillary, splenic, superior pancreatic and portal lymph nodes revealed severe necrotizing lymphadenitis, which was principally focal.

Further sections of the organs showed no specific lesions. The ulcerations in the stomach were all superficial, were accompanied by little cellular reaction and showed no specific features. Several sections of the rectus muscles showed normal-appearing muscle tissue with severe hemorrhage in the interstitium. No foci of necrosis or cellular exudation were seen.

Postmortem culture of the heart's blood in brain broth showed no growth. Cultures of the axillary nodes were contaminated. Pasteurella tularensis was recovered by culture from the areas of hemorrhage in the rectus muscles.

COMMENT

Clinical.—Of the 23 cases of tularemia occurring in the city of Cleveland during the year beginning April 1, 1938, all were in a period (November to March) in which rabbits are hunted or shipped in from

other sections for sale. The 3 fatal cases herein reported were definitely traced to the dressing of wild rabbits.

The incubation period was two and one-half to three and one-half days in 1 instance, five days in another and indeterminate in the third. The striking clinical characteristic of the primary lesions was their relatively benign appearance as contrasted with their painfulness.

The duration of illness in 2 of the patients was six days, while the other died on the tenth day. Foshay [1] reported that, of 74 patients with tularemia fatal within the first seven weeks, only 14 died within the first ten days of the disease. Most of the deaths in the published cases have occurred on the sixteenth day of the disease, but Simpson [2] reported that a patient died four days and seven hours after the onset. Additional cases in which death occurred within the first ten days and in which autopsies were performed have been reported by Palmer and Hansmann [9] (eight days), Archer, Blackford and Wissler [10] (eight days), Simpson [11] (ten days) and Grill [11] (ten days).

The clinical course in each of the cases herein described was characterized by hyperpyrexia, severe toxicity, delirium, coma and finally death. Icterus was present terminally in 1 case, while in another hemorrhagic tendencies were noted, with bleeding into the skin and subcutaneous tissues, regional lymph nodes and recti abdominis.

The laboratory findings were fairly constant in all cases. There was moderate leukocytosis, principally polymorphonuclear. Moderate anemia was present in only 1 case. The nonprotein nitrogen of the blood was slightly elevated terminally in the 2 cases in which it was determined. There was severe acidosis terminally in case 1, perhaps due to the sulfanilamide administered, although sodium bicarbonate had been given to forestall this contingency.

Agglutinations of Pasteurella tularensis were negative on admission in case 1 but were positive in dilutions up to 1:160 on the sixth day of illness. The patient, however, had received 800 cc. of whole citrated convalescent blood with a titer of 1:320 in the interim. The agglutinations were never positive in case 2. In the last case agglutinations were positive in dilutions to 1:320 on the tenth day of the disease. These results coincide with the findings of Foshay [12] and Friedewald and Hunt,[13] who found that a positive agglutination does not usually appear until the second week of the disease. The latter workers showed that the

9. Palmer, H. D., and Hansmann, G. H.: J. A. M. A. **91**:236, 1928.

10. Archer, V. W.; Blackford, S. D., and Wissler, J. E.: J. A. M. A. **104**: 895, 1935.

11. Cited by Foshay.[12]

12. Foshay, L.: J. Infect. Dis. **59**:330, 1936.

13. Friedewald, W. F., and Hunt, G. A.: Am. J. M. Sc. **197**:493, 1939.

injection of therapeutic antitularemic serum or even the percutaneous inoculation of the antigen may provoke a positive agglutination in nontularemic persons; however, the reaction was usually transient and did not rise as high as in case 1. It must also be considered that Friedewald and Hunt gave only 30 cc. of serum with an agglutination titer of 1:320, whereas in case 1 800 cc. of convalescent citrated whole blood of the same titer was used.

Therapy did not perceptibly alter the course in any of the patients. The use of sulfanilamide in case 1 is therefore of interest since only a single report of its use in tularemia has been found in the literature, that by Curtis.[14] In this report he attributed the cure of a patient with ulceroglandular tularemia to the oral administration of 15 Gm. (210 grains) of the drug two weeks after the onset of the disease. No studies of the blood levels of sulfanilamide were reported.

Pathologic.—The pathologic observations in these 3 cases correspond closely with those described in other cases in which death occurred within the first two weeks of the disease. The regional lymph nodes were the seat of focal necrosis, which microscopically was found predominantly in the sinuses. Some of the nodes had been almost completely destroyed by the necrosis. Hemorrhage into the nodes was seen in only 1 case, and in this there were widespread hemorrhages over the body. The nodes draining infected viscera were the seat of focal necrosis in each case, but they were less severely involved than the nodes draining the primary lesion. The essential feature disclosed by microscopic study of the lymph nodes was severe focal death of tissue. Necrosis, situated predominantly in the sinuses, had destroyed the nodes either focally or almost entirely. In some the process had ruptured through the capsule.

The lesions in the lungs consisted of focal necroses, 2 to 4 mm. in diameter; in 2 cases they were superimposed on a confluent basilar bronchopneumonia. In only 1 instance was there a larger focal area of necrosis. The margins characteristically blended with the surrounding tissues. The pneumonic exudate was made up principally of large mononuclear cells. The foci of necrosis were composed of cellular debris and nuclear fragments, and the collagenous and the elastic stroma of the septums were often the only identifiable structures. About the edges of the foci there were pale swollen mononuclear cells with eosinophilic cytoplasm containing vacuoles, nuclear fragments and red corpuscles and a moderate number of lymphocytes and desquamated alveolar epithelium but only a few polymorphonuclear leukocytes.

Essentially similar lesions were observed in the liver and spleen in all 3 cases. In addition there was marked hyperemia of the splenic pulp, with an increase in the number of polymorphonuclear leukocytes.

14. Curtis, W. L.: J. A. M. A. **113**:294, 1939.

Lesions of the gastrointestinal tract were confined to the gastric mucosa, where small superficial ulcerations had resulted in gross hemorrhage. Microscopic study in 1 case demonstrated a focal infiltration of lymphocytes and large mononuclears at the base of the ulcer, which is suggestive but not conclusive evidence of the specificity of the lesion.

The extensive hemorrhage into the rectus muscles in case 3 is interesting in the light of Simpson's [2] report of Zenker's degeneration in a patient dying at four and one-half days. Microscopic study of the muscle in case 3 revealed no lesions of a specific nature. However, cultures yielded Pasteurella tularensis.

SUMMARY

This is a clinical, pathologic and bacteriologic report of 3 cases of ulceroglandular tularemia, fatal within the first ten days of illness. Treatment, including the use of sulfanilamide, of specific immune serum and of convalescent serum, was not effective. Pasteurella tularensis was not found in the circulating blood but was recovered post mortem from lymph nodes in 2 cases and from the hemorrhagic mass in the rectus muscles in the third. Bacterial stains failed to reveal this organism in tissue sections. The lesions in lymph nodes, spleen, liver and lungs were characteristically those of a necrotizing inflammation, in which large mononuclear cells, often actively phagocytic, predominated.

INCIDENCE OF INDUCED PULMONARY TUMORS IN SUSCEPTIBLE MICE RAISED IN DUST-FREE AIR

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Early reports (Haaland;[1] Tyzzer[2]) describing primary pulmonary tumors in mice called attention to the presence of areas of "chronic inflammatory hyperplasia" (i. e., scattered and grouped lymphocytic infiltration) in the lungs of older mice which may be involved in the genesis of spontaneous tumors of the lungs in this species. It has also been suggested (Murphy and Sturm[3]) that tar painting produces pulmonary tumors in mice through the inhalation, ingestion or absorption of tar or through the general lowering of resistance which enables an inhaled irritant to produce pulmonary tumors with greater ease. Some investigators are of the opinion that inhaled dust particles are of prime importance even in the induction of tumors of the lungs following subcutaneous injection of 1,2,5,6-dibenzanthracene. Campbell[4] has expressed this view as follows: "We believe that the stimulus to start the tumor is inhaled in dust from the external environment."

Numerous experiments on the induction of pulmonary tumors in mice in this laboratory (Andervont[5]) have suggested that these neoplasms arise from direct contact of the carcinogen with the genetically susceptible pulmonary tissue of the animals and that no external adjuncts, such as atmospheric dusts, need be involved in the genesis. It is suggested that the increase in tumors of the lungs in mice exposed to dust containing tar and to other dusts is probably due to the presence of a carcinogenic agent in the dust rather than to the nonspecific irritation of noncarcinogenic particles. In this connection it has been found

From the National Cancer Institute, United States Public Health Service.

1. Haaland, M.: Fourth Scientific Report of the Imperial Cancer Research Fund, London, 1911.

2. Tyzzer, E. E.: J. M. Research **21**:479, 1909.

3. Murphy, J. B., and Sturm, E.: J. Exper. Med. **42**:693, 1925.

4. Campbell, J. A.: J. Indust. Hyg. & Toxicol. **19**:449, 1937.

5. Andervont, H. B.: Pub. Health Rep. **54**:1512, 1939.

(Shimkin [6]) that the intratracheal injection of 0.1 mg. of methylcholanthrene or of 1,2,5,6-dibenzanthracene will produce tumors in the lungs of strain A mice within five months. However, when susceptible mice (strain A back cross) were kept for a period of eight to twelve months on a bedding of 80 to 100 Gm. of mixed sawdust to which was added weekly 20 cc. of an aqueous–olive oil emulsion containing 8 mg. of 1,2,5,6-dibenzanthracene, no pulmonary tumors were induced by this procedure (Lorenz [7]).

In order to investigate the possible role of atmospheric dust in the genesis of induced pulmonary tumors in mice, it was decided to raise and maintain mice in a relatively dust-free atmosphere and to compare the incidence of pulmonary tumors induced by 1,2,5,6-dibenzanthracene in this group with the incidence of pulmonary tumors in similar animals kept under normal conditions. If atmospheric dust causes or influences the production of tumors of the lungs, an appreciable difference should be evident between the two groups.

EXPERIMENTAL STUDIES

Investigations designed to elucidate the importance of dust in the production of pulmonary tumors in mice can produce a decisive answer only if the dust in the space in which the animals are raised is kept at the lowest obtainable value. A number of factors, which are discussed later, prevent this value from being zero even if air free of dust is admitted to the space in which the animals are maintained. The experimental problem is therefore twofold: the purification of air so that the lowest possible dust content is admitted to the animals, and the control of the dust produced by the animals themselves, by the food or by the bedding.

Factors in Filtration of Air.—The dust of normal outdoor air or of air in well ventilated rooms is composed of particles approximately 50 per cent of which are between 0 and 0.5 micron in diameter, 40 per cent between 0.5 and 1 micron and a remaining few per cent between 1 and 2 microns. A different frequency of size prevails in industrial dust, in which the bulk of the particles is between 0.5 and 2 microns in diameter (Bloomfield [8]). Dust recovered from human lungs shows chiefly particles between 1 and 3 microns in diameter; only 13 per cent have a size of less than 0.5 micron (Bloomfield [8]). According to Drinker and Hatch,[9] "The silicosis producing dusts are retained to a greater extent than are very finely divided suspensions," which seems to indicate that the coarser particles are retained more effectively than the smaller ones. According to Shaw and Owens,[10] only 25 per cent of the particles measuring 0.5 micron are retained in the lungs. As the size of toxic dust particles in industrial plants, e. g., silica, is

6. Shimkin, M. B.: Am. J. Cancer **35**:538, 1939.

7. Lorenz, E.: Unpublished data.

8. Bloomfield, J. J.: Pub. Health Rep. **42**:961, 1933.

9. Drinker, P., and Hatch, T.: Industrial Dust, New York, McGraw-Hill Book Company, 1936.

10. Shaw, N., and Owens, J. S.: The Smoke Problem of Great Cities, London, Constable & Co., Ltd., 1925.

usually considerably larger than 0.5 micron, commercial air filters are considered adequate if they filter out these larger particles efficiently. The particles smaller than or equal to 0.5 micron consist mainly of fumes (e. g., smoke from chimneys) and small mineral matter.

Although in human lungs only about 25 per cent of the particles smaller than or equal to 0.5 micron are retained, it cannot be concluded that this also is true for lungs of small animals, such as mice, in which the air passages are extremely small in comparison with those of human lungs. Furthermore, if dust is essential for the development of pulmonary carcinoma, no *a priori* statement can be made concerning the kind of dust or fumes and the size of the particles.

Therefore, for the experimental work in question, air has to be filtered to such a degree that it is essentially free from fumes and dust particles of all sizes.

Industrial filters usually consist of paper, cloth or fibers such as steel wool, glass wool or hemp. These materials may be oiled to increase their efficiency. The chance of such filters to remove particles smaller than or equal to 0.5 micron, especially fumes, is relatively poor.

The most efficient device, the electrostatic precipitator (Drinker and Hatch[9]), will retain all dust particles of any size if operated under adequate conditions; under these conditions, however, it generates nitrous oxides and especially ozone in toxic amounts.

Numerous methods have been devised for measuring the amount of dust in air; they have in common that either the amount of dust in a certain volume of air is weighed or the number of dust particles is counted. In the present investigation completeness of data necessitated daily dust counts of the outside air, of the filtered air and of the air in the space in which the animals were raised. The Bausch and Lomb dust counter (fig. 1) was chosen as the measuring instrument because it permits rapid measurements and can be easily adapted to the determination of dust content in a closed system without its function being interfered with. In the Bausch and Lomb counter a given amount of air the dust content of which is to be measured is impinged, through a slit, on a glass disk by the rapid action of a small pump of 28.3 cc. volume. The particles are counted in a dark field illuminator which probably visualizes particles of sizes down to 0.05 micron. Its efficiency with a slit of 0.1 mm. and a pump of 28.3 cc. is approximately 98 per cent. By replacing the 28.3 cc. by a 100 cc. pump and thus increasing the impinging velocity, an efficiency of better than 99 per cent is obtained. The increased impinging velocity with the 100 cc. pump may occasionally cause large particles to be broken up at the edges of the slit, thus producing too high a dust count. For this reason the 100 cc. pump gives an upper limit for the amount of dust present in the sample. The Bausch and Lomb dust counter is primarily designed for work in the open air but can be adapted easily to taking dust counts in a closed system by connecting the intake of the counter to the system by means of a rubber hose and pumping air from the system into the counter with the aspirator bulb, or, if the air is flowing through the system, by letting the air pass through the counter. A rubber hose about 50 cm. long with a bore of 6 mm. produces an error in the dust count of approximately —10 per cent, as some particles stick to the rubber hose. The zero count of the dust counter was checked with an electrostatic precipitator as described by Drinker and Hatch.[9] It consisted of a pyrex tube with an effective length of 23 cm. and an inner diameter

11. Footnote has been deleted.

of 3 cm. It was operated at approximately 18,000 volts r.m.s. With a flow of 4 liters per minute, the Bausch and Lomb counter gave a zero count for the filtered air.

As the electrostatic precipitator offers no resistance to the air flow, the air pressure inside a counter that is connected to it is the same as that of the outside air. If the air pressure is lower inside the system (this was the case in the experimental arrangements to be described later) there will be a lower pressure also inside the counter that is connected to the system. In the Bausch and Lomb counter simple rubber or metal valves are used, producing a small leakage of outside air (containing dust particles) into the interior of the counter if the pressure

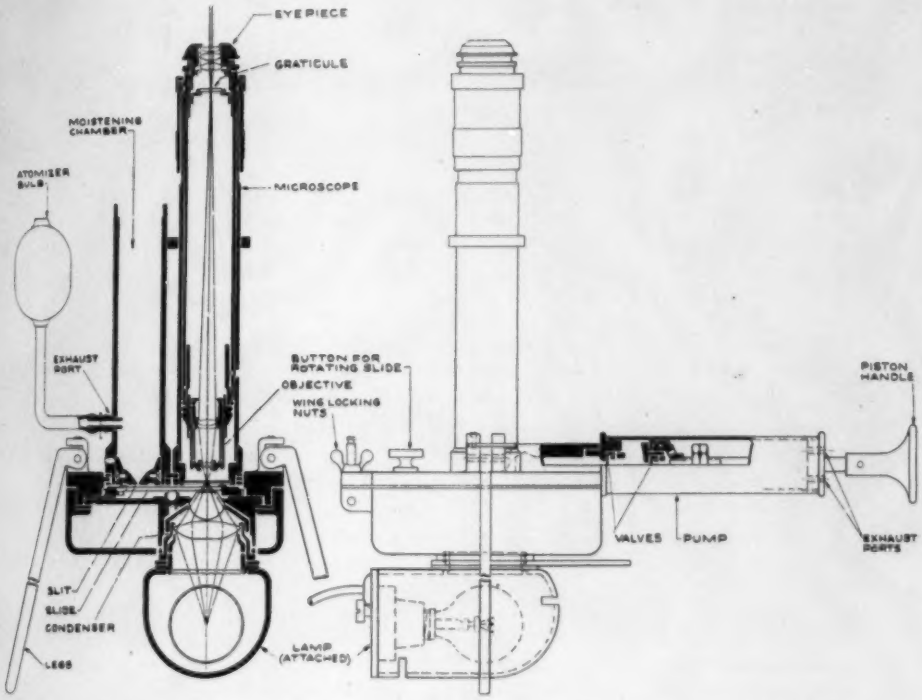

Fig. 1.—Schema of the Bausch and Lomb dust counter, published with the permission of the Bausch & Lomb Optical Company.

in the interior of the counter is lower. In operating the counter pump, a small amount of this dust will be precipitated on the glass disk. Its influence on the total dust count will increase with a decrease in the amount of dust particles present in the sample. This effect is erratic; from numerous measurements it is estimated to be about 3×10^4 particles per cubic foot when all valves are in good operating condition. This corresponds to 1 particle per field of the dust counter if the 100 cc. pump is used.

Experimental Dust Filters.—The electrostatic precipitator is the most efficient device for obtaining air free of dust. It could not be used, however, as the removal of ozone and nitrous oxides by chemical methods requires an elaborate

set-up, and solid adsorbents, such as charcoal, must be avoided because they represent a new source of dust. There remain the mechanical filters, such as porous materials, the pores of which retain the dust. The importance of the removal of fumes and smoke already has been pointed out. As mechanical filters are poor in removing fumes and smokes, they must be used in series with prefilters, such as gas mask canisters,[12] for the removal of smokes and fumes. Numerous filters of different materials were tried. The most efficient filter obtained consisted of filter paper (Whatman no. 1) coated with petrolatum. The filter paper was wound on a cylinder of galvanized wire screen (7 mm. mesh) 30 cm. long and 6 cm. in diameter; four additional layers of untreated filter paper were wound on top of it. The ends of the cylinder were closed by rubber stoppers, one of these carrying the outlet. The filter was enclosed in a glass tube with an inlet. The air, prefiltered by the canister, entered through this inlet, was then filtered by the filter paper and passed into the system.

The dust count in the room in which the investigation was carried out from October 1938 to March 1939 varied between 3 and 5×10^6 particles per cubic foot. Occasionally higher counts up to 10×10^6 particles per cubic foot were encountered. They occurred in winter, usually when a heavy smoke blanket covered the city. Lower counts occurring occasionally could frequently be traced to improper operation of the counter. The filter arrangement described reduced the count of the outside air to an average of one thirtieth. However, the filter resistance increased gradually to 5 cm. of mercury for a continuous flow of 4 liters per minute, probably owing to clogging of the pores of the filter. As the air was pumped through the system in which the mice were raised, it did not seem advisable to have the experimental animals live at a pressure considerably lower than the pressure under which the control animals were kept.

An investigation was started, therefore, for a new type of filter having a lower resistance than the petrolatum-coated filter paper and possibly higher efficiency. This filter was finally found in tightly packed glass wool wetted with 50 per cent aqueous sulfuric acid. The glass wool was packed into 4 Emerling towers (*F* in fig. 2) 50 cm. high and 3.8 cm. in diameter, connected in parallel. At an air flow of 4 liters per minute their resistance was 1.5 cm. of mercury; they reduced the outside dust count (3 to 5×10^6 particles per cubic foot) to one-hundredth and less — $\leqq 3$ to 5×10^{-4} particles per cubic foot. This count includes the background due to leakage of the counter, as mentioned previously. No detectable amount of acid was carried by the filtered air. Two thousand liters of filtered air was bubbled through 100 cc. of water; the addition of barium chloride solution gave no precipitate; the solution was still clear after several hours.

The lower resistance of this type of filter is due to the fact that sulfuric acid will form an extremely thin film on the glass fiber. Its high efficiency is probably due to the considerable wetting power of aqueous sulfuric acid in combination with a chemical action. Due to lack of time the efficiency of these filters in removing fumes and smokes was not determined. It was therefore connected in series with a canister (type G), and this combination was used during the final

12. Such canisters are Type SMH-2 and Type G, manufactured by the Mine Safety Appliance Company, Pittsburgh. According to the manufacturer, both types will remove sulfur dioxide (the air of Cambridge, Mass., contains approximately 5 parts sulfur dioxide in 10^6 parts of air). Type GMH2 will remove tobacco smoke to the amount of 60 per cent; Type G, to the amount of 100 per cent. For a continuous flow of 4 liters per minute the filters should be replaced approximately every month.

experiment from October 1938 to March 1939. The canister was replaced monthly. The glass wool filters were regenerated once by washing with 50 per cent aqueous sulfuric acid.

Raising Mice Under Dust-Free Conditions.—After the establishment of a source of air practically free of dust and fumes, the next step concerned the control of the dust produced by the animals or by the food or by the bedding. The animals were raised in 5 gallon (19 liter) glass jars covered by circular glass plates (fig. 3). The tip of the jars and the edge of the glass plates were ground flat and sealed airtight with bee's wax containing 10 per cent Venice turpentine.

The glass plate was provided with a central aperture and fitted with a rubber stopper, which carried the air inlet and outlet tubes, a tube for the connection with the dust counter and a tube for the water supply. A short rubber hose

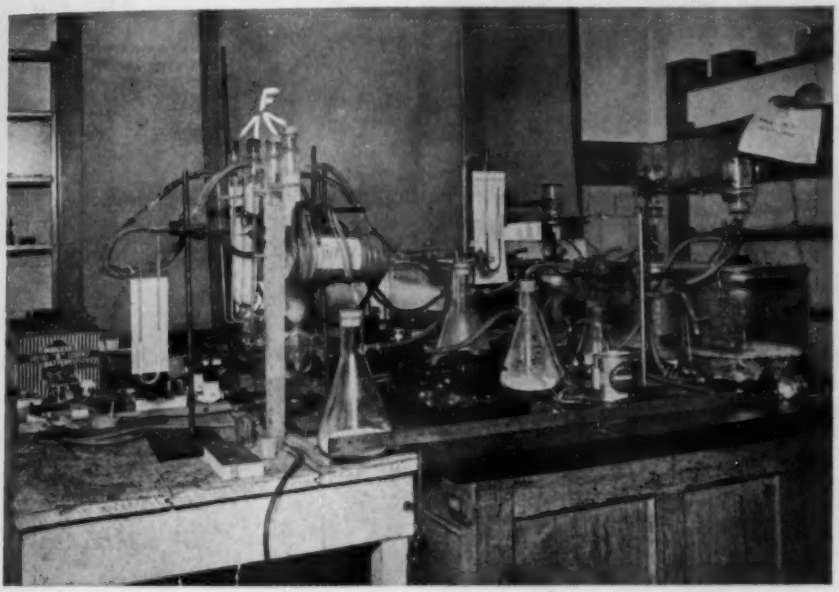

Fig. 2.—The apparatus as finally set up for use in the investigation.

connected this tube to the watering bottle; by clamping this rubber hose, the watering bottle could be refilled.

The mice lived on a 3 mm. mesh wire netting of stainless steel approximately 4 cm. above the bottom of the jars. The mesh netting was sufficiently wide to permit feces to fall through to the bottom of the jar, which was covered with a layer of silica gel 14 to 20 mesh, 1 to 2 cm. high, to absorb urine and moisture. It was important to control the humidity in the jars and to keep it well below saturation, so that sudden changes in temperature could not cause a condensation of water vapor which would plug up the outlet tubes for the air flow. The food—Purina dog chow [13]— was kept in food hoppers made of 7 mm. mesh gal-

13. According to the manufacturer, the composition is as follows: protein, 20 per cent; fat, 3 per cent; carbohydrates, 56 per cent; ash, 6 per cent; water, 15 per cent. It contains vitamins A and G and is pressed to convenient checkers.

vanized wire screen. Dust originating from this food presented a serious difficulty, which was finally overcome by soaking the food in warm lard for several hours. All metal parts in the jars were oiled with liquid petrolatum so that dust would stick to them. At the same time the fur of the animals became covered with a slight coat of oil from contact with the liquid petrolatum and the lard on the food, minimizing the amount of dust from the skin and the fur. Another serious problem was the choice of a dust-free material for bedding for the litters. Fine strips of waxed paper finally proved to be most satisfactory.

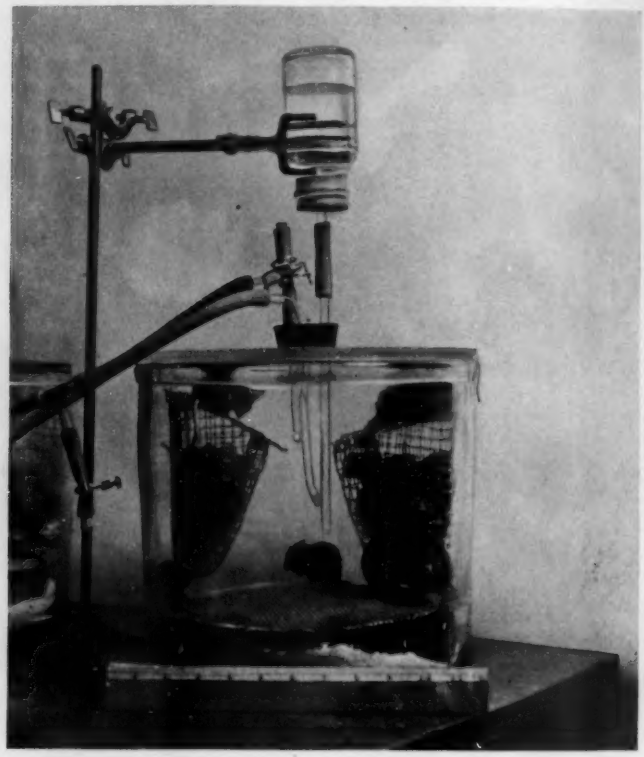

Fig. 3.—The living quarters of the experimental animals.

With these precautions the amount of dust in the jars was kept at a low value, on an average $\leqq$ 3 per cent of the amount of dust in the outside air. As the air entering the jars was practically free of dust, the small amount of dust that could be inhaled by the animals consisted of food fragments (mainly fiber) and particles from the skin and fur and from the feces that had not dropped onto the silica gel.

Operation of Apparatus.—By keeping mice in a closed jar and determining the time at which they began to suffocate, it was demonstrated that a supply of filtered air of 1 liter per minute was amply sufficient for 10 to 12 mice. A larger air flow would be undesirable as it might stir up dust within the jars. The filtered air was pumped through the jars, because a slightly lower inside pressure kept

the glass plates tightly pressed against the rim of the jars and because suction pumps can be made to operate at a low number of revolutions (300 per minute) favorable for continuous operation. Three small pumps driven by geared-down motors [14] were used, each having a pumping speed of 4 to 4.5 liters per minute at atmospheric pressure. A calibrated flow meter in the inlet line indicated the proper operations of the pumps. Two of the pumps were driven by the power supply of the laboratory, each being used alternately for twenty-four hours. A mercury switch with a battery operated relay would connect the other pump in case the running pump went out of operation. The third pump was operated by a 6 volt storage battery of large capacity and went into operation (by mercury switch and relay) if the power supply of the laboratory failed. All connections were made of pyrex glass and rubber hose. Before use, the rubber hose was cleaned with benzene and boiled in water, and the inside of the glass and rubber tubing was coated with a thin film of petrolatum. At the beginning of the experiment rubber hose of pure gum rubber was used; this was replaced later by Duprene rubber hose, which is not attacked by petrolatum.

Figure 2 shows the experimental apparatus in its final form.

The outside air, after superficial drying with anhydrous barium perchlorate, passed through the prefilter (type G canister) and then through the main filter, consisting of 4 Emerling towers in parallel containing glass wool wetted with 50 per cent sulfuric acid. Behind the main filter it entered a large filtering flask through a glass tube reaching to approximately 1 cm. above the bottom of the flask. The petrolatum-coated bottom, deflecting the air flow, acted as an additional filter. It then passed through the flow meter, branched into four currents of approximately the same flow (1 liter per minute for each branch) and entered the four jars through glass tubes reaching to the middle of the jars and bent sideways at their ends. T joints to which the dust counter could be connected were inserted between the filtering jar and the flow meter. By clamping the line between the T joints the air current could be passed through the dust counter.

The air left the jars through outlets close to the top; these outlets were connected by short rubber tubings to small filtering flasks filled partly with silica gel, to collect condensed water in the outlet tubes. Behind these flasks the four outlet lines were united into one line carrying the mercury switches which would close the relay circuit when the difference in air pressure between the outside air and the air in the system fell below a certain value. Behind the mercury switches the air line branched again into three lines leading to the three pumps. Before entering the pumps, the air was dried with anhydrous barium perchlorate to prevent the collection of water in the pumps.

Animal Experiments.—After a number of mishaps and failures, it was possible to raise 8 litters consisting of 43 mice. Mice of strain A and hybrids derived by mating strain A to strain C_3H or strain C57 black mice were used. Previous investigations showed (Andervont [15b]) that the first generation hybrids derived from strain A animals are as susceptible to the induction of pulmonary tumors as are the strain A parent mice. Pregnant females were placed in the jars, and there the offspring were born and nursed for one month, until they reached the weaning age. When the young were weaned, the mothers were discarded, and the sexes were separated and returned to separate jars, where they remained until the time of the injections. The jars were cleaned six times after the mice had received the injections. During the time of weaning, receiving injections and

14. The type used was the W. M. Welch Scientific Company no. 1410A modified.
15. Andervont, H. B.: (*a*) Pub. Health Rep. **52**:212 and (*b*) 304, 1937.

cleaning, the mice were kept in wooden boxes which did not contain any bedding, and the total time the experimental mice were kept under ordinary atmospheric conditions was about ten hours. The animals born and raised in the dust-free chambers were in excellent health throughout the course of the experiment.

Controls consisted of mice of the same age and derivation which lived in wooden boxes with sawdust bedding, kept in the room where the dust-free chambers were located. Repeated dust counts in these boxes showed that the number of particles when the animals were moderately active was somewhat lower than that of the outside air.

All experimental and 19 control mice were born between Oct. 7 and Nov. 8, 1938; 11 controls were born Nov. 25, 1938. The injected material consisted of 0.8 mg. of 1,2,5,6-dibenzanthracene dissolved in 0.2 cc. of lard and was given subcutaneously in the right axilla. This procedure is known (Andervont[18]) to induce pulmonary tumors in practically all strain A mice and their F_1 hybrids within three months. The experimental and 19 control animals were given injections on Dec. 16, 1938; the remaining 11 controls were given injections on Jan. 16, 1939.

RESULTS

Three months after the injection of the carcinogen the mice were killed and examined for the presence of macroscopic pulmonary tumors. The results are summarized in the table.

Summary of Experimental Results

Mice Used	Number of Mice Used	Mice in Which Macroscopic Pulmonary Tumors Developed
Strain A	9	8
Hybrids obtained by mating strain A with strain C3H	17	17
Hybrids obtained by mating strain A with strain C57 black	17	17
Strain A (control)	5	5
Hybrids obtained by mating strain A with strain C3H	17	15
Hybrids obtained by mating strain A with strain C57 black	8	8

It is seen that 42 of 43 experimental mice and 28 of 30 control mice had macroscopic pulmonary tumors. The number of tumors in each pair of lungs varied from 1 to 20, with no appreciable difference between the experimental and the control animals. In 4 of the experimental mice subcutaneous tumors had developed at the sites of injection. It is therefore apparent that mice born and kept in an atmosphere in which the dust content was $\leqq 3$ per cent of the dust content under which the control animals lived (3 to 5×10^6 particles per cubic foot) had as many tumors in their lungs following subcutaneous injection of 1,2,5,6-dibenzanthracene as did the controls. The experiment corroborates the presumption that atmospheric dust does not play the chief role in the genesis of primary pulmonary tumors induced in mice.

SUMMARY

A method for producing dust-free air (dust content $\leqq 1/100$ of that of outside air) is described.

An experimental apparatus in which it is possible to raise mice for any period of time in closed jars and control the amount of dust in these jars to $\leqq 1/30$ of that of outside air is described.

Mice born and kept in the experimental apparatus were as susceptible to the induction of pulmonary tumors by subcutaneous injection of 1,2,5,6-dibenzanthracene as were mice of the same genetic constitution which were kept in the outside air.

METAPLASIA OF THE EPITHELIUM OF THE PROSTATIC GLANDS, UTRICLE AND URETHRA OF THE FETUS AND NEWBORN INFANT

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AND
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NEW YORK

Fraenkel and Papanicolaou [1] described the massive hypertrophy of the vaginal epithelium of the human fetus during intrauterine life and the extensive desquamation which follows delivery. They suggested that these are manifestations of the action of an estrogenic hormone derived from the blood of the mother across the placenta. No similar detailed study of the male fetus has been made in which a masculine counterpart of the vaginal changes in the female has been described. The utricle and prostatic urethra are considered homologues of the vagina (R. Meyer [2]; Vilas [3]). Squamous metaplasia has been experimentally brought about in these structures by the use of estrogens in mice (Lacassagne [4]), in mice and rats (de Jongh [5]), in monkeys (Parkes and Zuckerman [6]), in adult human subjects (Moore and McLellan [7]), in cats (Starkey and Leathem [8]) and in the newborn opossum (Burns [9]).

Schlachta [10] described, in the development of the human prostate, the appearance of epithelium of a pavement type in the glands in a 38 cm. fetus and in a number of full term fetuses and newborn infants. Schlachta found that this metaplasia disappears by the end of the second extrauterine month. Also, the change was absent in a 31 cm. fetus. Pallin [11] pictured squamous metaplasia in the prostatic utricle in an even younger fetus, measuring 26 cm. Meyer [2] described pavement epithelium in the utricles of fetuses of 4 and 5 months.

From the Department of Laboratories, Beth Israel Hospital.

1. Fraenkel, L., and Papanicolaou, G. N.: Am. J. Anat. **62**:427, 1938.
2. Meyer, R.: Arch. f. mikr. Anat. **74**:844, 1909.
3. Vilas, E.: Ztschr. f. Anat. u. Entwcklngsgesch. **99**:599, 1933.
4. Lacassagne, A.: Compt. rend. Soc. de biol. **113**:590, 1933.
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11. Pallin, G.: Arch. f. Anat. u. Entwcklngsgesch. (Anat. Abt.), 1901, p. 135.

Stieve [12] described squamous epithelium occurring in the prostate of the newborn infant, as did also Peter.[13] However, in anatomic studies on the embryonic development of the prostate Ruedinger,[14] Tourneux [15] and Lowsley [16] did not mention this change. Moore,[17] in his description of the development of the fetal prostate (based on a study of 8 cases) made no mention of such squamous metaplasia or of its regression during extrauterine life. In a subsequent paper Moore and McLellan [7] compared the changes experimentally produced in man by estrogens to the naturally occurring metaplasia of the fetus, suggesting that the latter is also due to the action of estrogens. Vintemberger [18] described the utricle of the newborn as a cavity lined with stratified pavement epithelium which changed to polyhedral cells during infancy. Vilas' [3] thorough study of the embryonic development of the human prostatic utricle stopped at a stage too early for the change to have been observed.

We have studied prostates from 62 fetuses and infants, representing various stages of development from the tenth fetal week to the sixth month of extrauterine life. Of these fetuses and infants, 24 were stillborn and varied in crown-heel length from 2.5 to 54 cm.; 38 were liveborn, and lived for periods of from ten minutes to six months. Of the latter group, 9 were less than 45 cm. in crown-heel length and might therefore be considered premature. They survived for from three hours to fourteen days.

In the youngest fetuses available, only the ductus deferentes and the utriculus were recognizable. By the fourth month the prostatic glands were present as solid cords, which in a few instances showed the beginning of the formation of lumens. The first squamous metaplasia was observed in a 23 cm. fetus, estimated as about 4½ months old (fig. 1*A*). At a single level of the utricle the center was completely filled with a mass of squamous cells. In this prostate, although the glands farthest from the urethra appeared as solid cords, those closer showed definite lumens, and a few contained an eosinophil substance. In the prostate of a 26 cm., 5½ month fetus, in which the utricle was lined with partly

12. Stieve, H.: Männliche Genitalorgane. Die Vorsteherdrüse (Prostate), in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie der Menschen, Berlin, Julius Springer, 1930, vol. 7, pt. 2, pp. 247-249.

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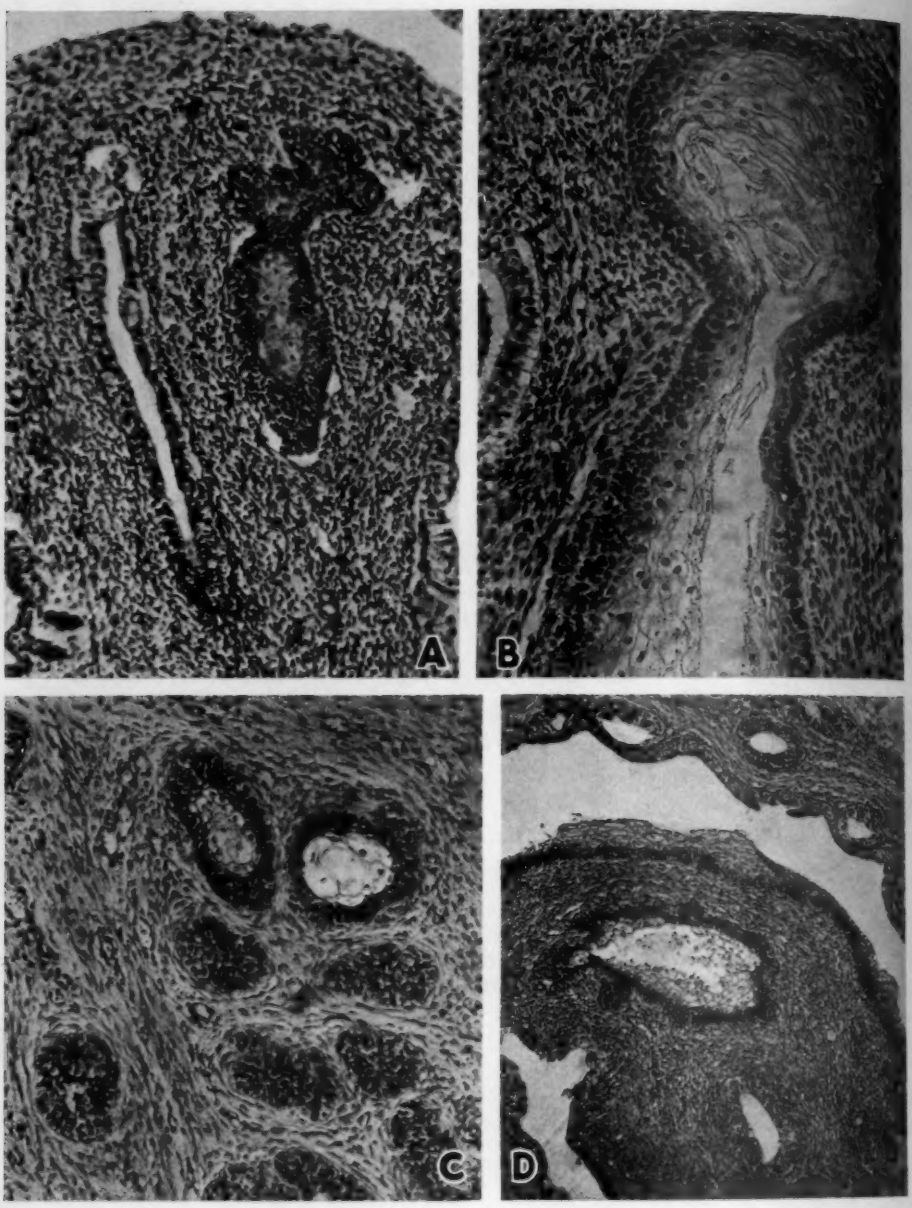

Fig. 1.—*A*, (4½ month fetus, 23 cm. crown-heel length), lumen of utricle completely filled with squamous cells. *B*, (5½ month fetus, 27 cm. crown-heel length), more extensive squamous metaplasia in utricle. *C* (5½ month fetus, 26 cm. crown-heel length), earliest instance of squamous metaplasia in prostatic glands found in present series. *D* (fetus, 30 cm. crown-heel length), squamous cells lining portions of prostatic urethra and prostatic utricle. Ventral structures are up and dorsal ones down.

cornified squamous epithelial cells, many of which were desquamated into the lumen, a few of the prostatic glands showed squamous cells filling their centers (fig. 1*C*). Squamous epithelium lining portions of the prostatic urethra was first seen in a 30 cm. fetus (fig. 1*D*). The utricle showed extensive squamous metaplasia of the epithelium. Squamous change was seen in only a single prostatic gland.

In the prostate of every stillborn fetus 23 cm. in crown-heel length or larger, metaplastic change was found in the utricle, the prostatic urethra or the prostatic glands. In the older fetuses the changes in the glands, urethra and utricle were sometimes very marked. Most frequently involved were the glands and ducts in closest proximity to the urethra and utricle, usually situated dorsal and slightly lateral to the urethra. Not infrequently, however, a group of glands situated ventral to the urethra was completely lined with squamous epithelium, and occasionally glands at the most peripheral and ventral portion of the organ showed extensive squamous metaplasia. In fetuses 46 cm. in length and larger the production and desquamation of squamous cells in the utricle were sometimes so excessive as to produce considerable distention of that organ. The utriculus in some instances became large enough to bulge into the urethra in the region of the colliculus, and was grossly visible (fig. 2). In several instances the distention was sufficient to have interfered with drainage from the bladder. Of the 7 infants in whom considerable distention of the utricle was noted, 4 were stillborn and 3 were infants who had lived three days or less. They varied in length from 46 to 54 cm.

In the stillborn full term fetus and in a number of infants living from a few hours to several days, we noted focal changes such as Moore [17] described in his discussion of the histologic character of the prostate of the infant. In such focal hyperplasia of the glands "the acini are lined by a very tall columnar cell with clear cytoplasm and definite cell membranes. The nuclei are relatively small and basal, and a basal layer of cells cannot be differentiated." Cells of this type are not seen in older children, nor are they found in all infants close to term. However, as the glands were not cut serially, small focal hyperplastic areas might have been missed.

Schlachta [10] described similar changes in the mature fetus and in the newborn infant. He demonstrated, and we can confirm his observation (fig. 3*A*), that these cells give a positive mucicarmine stain and that the lumens of such glands contain an amorphous substance which also stains pinkish red in the mucicarmine stain.

Fraenkel and Papanicolaou [1] described the striking involutionary change in vaginal epithelium occurring within a few hours after birth of the female infant. We have sought similar changes in the epithelium

of the prostatic glands, utricle and prostatic urethra of the male infant. The metaplasia in the male infant does revert, but not as sharply as in the female. During the first two postnatal days we could recognize little

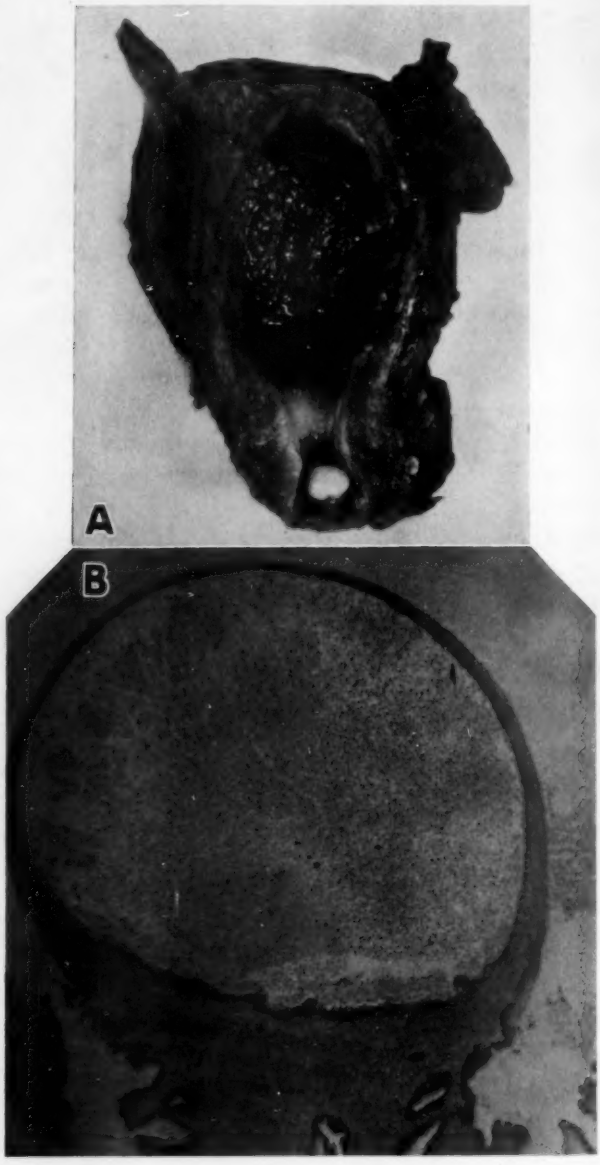

Fig. 2.—*A* (fetus, 54 cm. crown-heel length), verumontanum protruding into prostatic urethra, obstructing outflow from urinary bladder. *B* (fetus, 54 cm. crown-heel length), section through greatly distended utricle, showing lumen filled with desquamated cells. Ventral structures are up and dorsal ones down.

or no evidence of regressional changes. During the third or fourth day we observed in some instances desquamation of the epithelium, together with swelling of the epithelial cells and in some instances formation of intraepithelial cysts (fig. 3 *B*). Beneath the squamous epithelium there begins to form a pseudostratified, transitional type of epithelium. In time, all the squamous epithelium is shed and is seen lying in the lumen. Cornified remnants remain for a considerable time.

In the prostate of a 5 day old, full term infant no evidence of regressive changes could be made out. In all prostates from infants living a week or longer, including 3 who were premature, measuring 38, 41 and 43 cm., respectively, evidence of regression was present. In the prostate of an 11 day old infant regression was marked (fig. 4 *A*), as it was in that of a 16 day old infant (fig. 4 *B*). At 27 days remnants of squamous cells were found within the lumen of a gland in which the epithelium had otherwise entirely reverted to the infantile type (fig. 4 *C*). In the prostates of infants of 1 month (fig. 4 *D*) and of 10 weeks the epithelium had reverted to the transitional type but showed a few intraepithelial cysts. Cornified cells were seen in the lumen of the utricle.

There were 5 prostates from infants over 3 months of age. Three of these no longer showed any evidence of squamous metaplasia. Two, from infants 4 and 5 months of age, showed as marked metaplasia as was seen in any fetal prostate in the entire series. However, these infants gave evidence of a severe deficiency of vitamin A, for both showed cystic fibrosis of the pancreas (Andersen [19]) with secondary metaplasia of epithelium in many other organs. Therefore, the squamous metaplasia in these prostates is interpreted as being part of the general reaction to vitamin A deficiency. It is interesting to note in this connection that Schmidt [20] described squamous metaplasia with cornification in the glands of the prostate and in the utriculus of a 5 month old infant with keratomalacia and malnutrition.

In the light of the experimental work on animals in which it has been shown that estrogens will produce squamous metaplasia in the male homologues of the vagina (see an earlier paragraph), it is reasonable to ascribe such changes found in the human male fetus and the newborn to circulating estrogens derived through the placenta from the mother. Philipp [21] demonstrated the presence of estrogens in the urine of newborn males during the first three days of extrauterine life. Soule [22] found equal concentrations of estrogens in maternal and fetal blood.

19. Andersen, D. H.: Am. J. Dis. Child. **56**:344, 1938.
20. Schmidt, J. E.: Beitr. z. path. Anat. u. z. allg. Path. **40**:120, 1907.
21. Philipp, E.: Zentralbl. f. Gynäk. **53**:2386, 1929.
22. Soule, S. D.: Am. J. Obst. & Gynec. **35**:309, 1938.

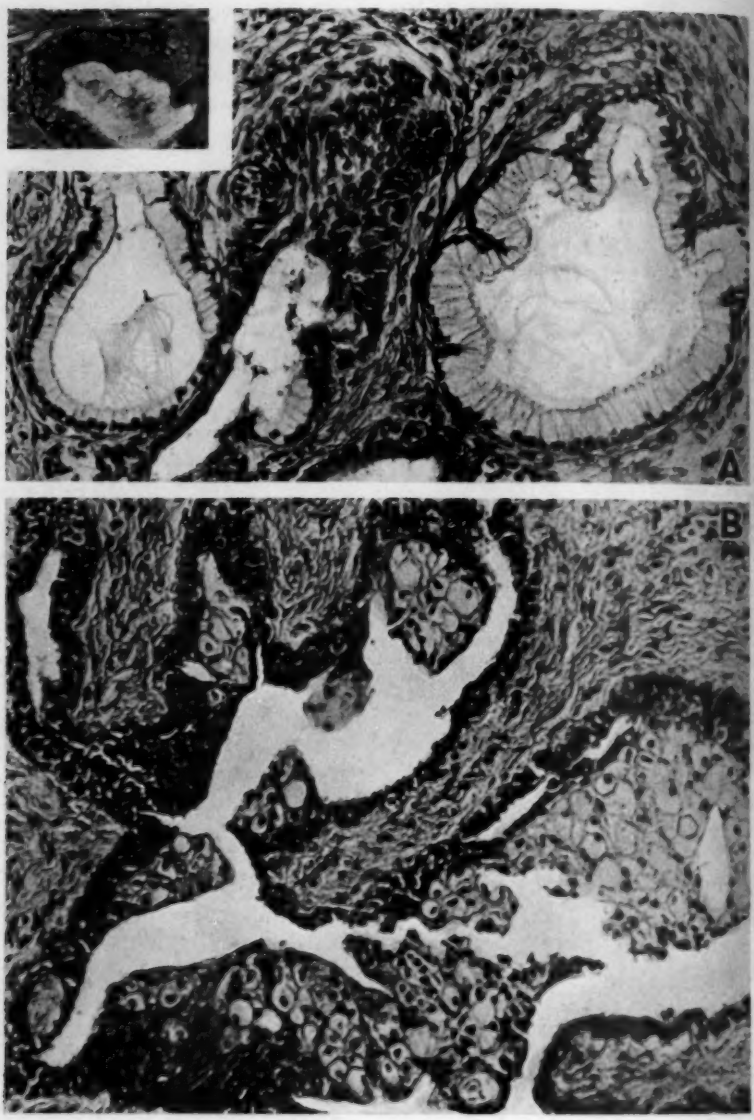

Fig. 3.—*A* (fetus, 48 cm. crown-heel length), focal hyperplasia in prostatic gland. Note single-layered epithelium with basilar nuclei and clear cytoplasm. The inset (newborn 2 days old, 48.5 cm. crown-heel length; mucicarmine stain; orthochromatic film and yellow filter) shows the fine granulation in the cells and the black staining at the luminal border. In the original slide these are pink and bright red, respectively. The corresponding section stained with hematoxylin and eosin shows mucinous epithelium as seen in *A*. *B* (newborn 3½ days old, 50 cm. crown-heel length), gland showing swollen squamous cells, dehiscence and desquamation. Ventral structures are up and dorsal ones down.

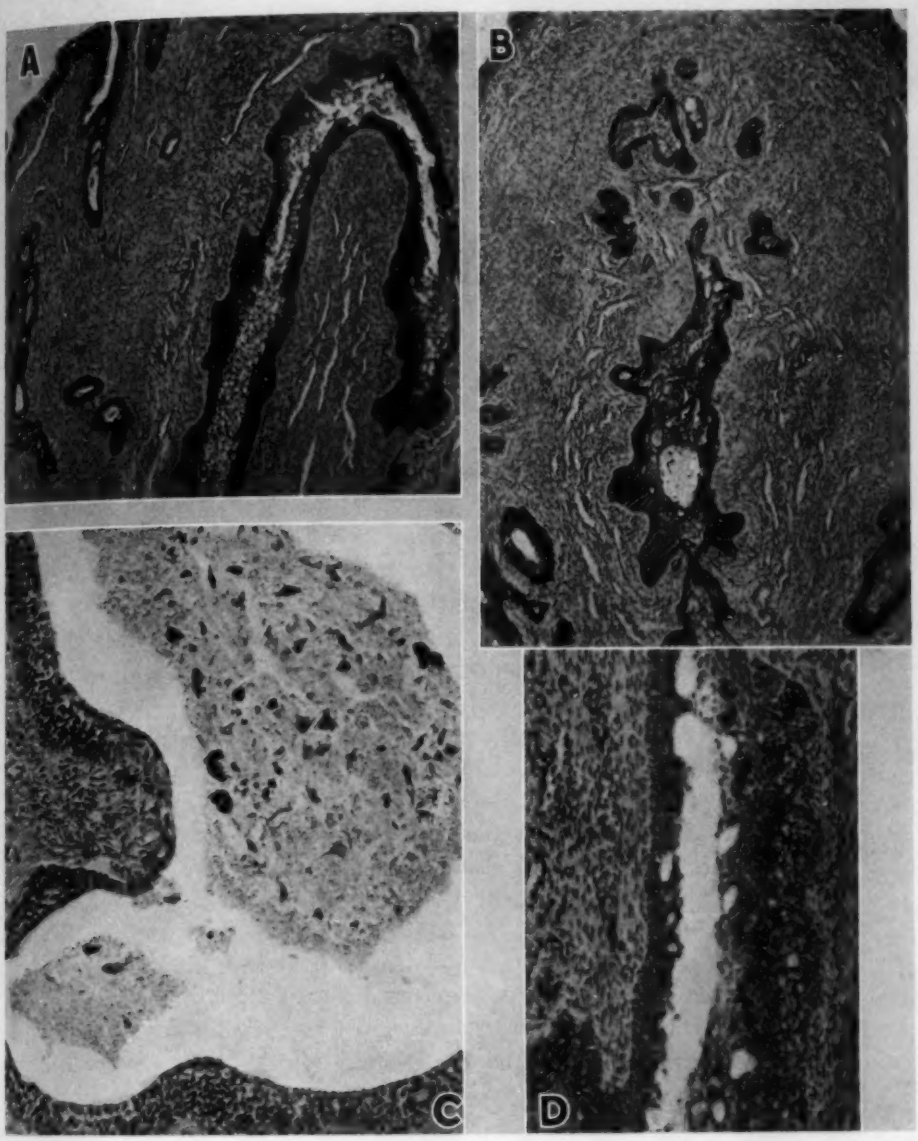

Fig. 4.—*A* (newborn 11 days old, 50 cm. crown-heel length), utricle showing marked regression from metaplastic state. The lumen is filled with desquamated cells. The lining epithelium, still showing a few "cystoid" areas, is almost entirely reverted to the infantile type. *B* (newborn 16 days old, 50 cm. crown-heel length), further regressional changes in utricle and glands. *C* (infant 27 days old, 50 cm. crown-heel length), distended gland lined with typical epithelium of infantile type. The lumen contains remnants of desquamated squamous cells. *D* (infant 4 weeks old, 45 cm. crown-heel length), almost complete reversion to normal transitional epithelium. Ventral structures are up and dorsal ones down.

Fraenkel and Papanicolaou [1] suggested that the changes in the vaginal epithelium of the female fetus are due to the action of maternal estrogens, though allowing for the possibility that at full term the stimulated ovaries of the fetus may themselves produce a certain amount of estrogen.

The question arises why the metaplastic change in the vaginal and prostatic epithelium does not occur as soon as these structures are differentiated. There are a number of possible explanations. First, the indifferent anlage may not be sensitive to the action of estrogens, and metaplasia must await differentiation of definitive epithelium. Second, the development of metaplasia may require a long period of stimulation by estrogens. This explanation is suggested by the several months that are required in some animals to produce the change (Lacassagne [4]; Burrows and Kennaway [23]). Third, the concentration of the circulating estrogens in the vicinity of the developing structures in the fetus may not have reached the necessary threshold. It is known (Cohen, Marrian and Watson [24]) that there is a gradual and fairly steady increase in the amount of estrogenic substance excreted during pregnancy, reaching its peak in the last trimester. Goldberger [25] showed that the excretion of free estrogen is highest between the thirty-second and fortieth weeks. Smith and Smith [26] stated that the level of serum estrogen rises rapidly during the last trimester.

The marked distention of the utricle seen in some of the mature and postmature fetuses may be correlated with high levels of circulating estrogens. Similar cases have been described by English [27] and Springer.[28] Bugbee and Wollstein [29] described hydronephrosis in a number of infants, which they explained on the basis of swelling in the region of the verumontanum, with urethral obstruction. Histologic studies were reported in only a single case, so that it is not certain whether the underlying change was the same as that reported here. Burrows and Kennaway,[23] in their description of experimental lesions produced in mice, mentioned obstruction to urinary outflow.

We have seen and described two types of histologic change appearing in the development of the prostate of the fetus and the newborn. One is metaplasia to a squamous type of the epithelium of the glands and

23. Burrows, H., and Kennaway, N. M.: Am. J. Cancer **20**:48, 1934.
24. Cohen, S. L.; Marrian, G. F., and Watson, M.: Lancet **1**:674, 1935.
25. Goldberger, M. A.: Am. J. Obst. & Gynec. **33**:1093, 1937.
26. Smith, O. W., and Smith, G. V.: Am. J. Obst. & Gynec. **33**:365, 1937.
27. English, V.: Med. Jahrb. **3**:61, 1873.
28. Springer, C.: Ztschr. f. Heilk. **19**:459, 1898.
29. Bugbee, H. G., and Wollstein, M.: J. Urol. **10**:477, 1923.

ducts, also occurring in the epithelium of the prostatic urethra and utricle. This change occurred in all subjects examined larger than 23 cm. It is in all probability caused by estrogens derived by way of the placental vessels, for an almost identical change has been produced in animals and in man by administration of estrogens. These substances occur in increasing amounts in the maternal (and presumably the fetal) circulation after the third month of gestation.

A second change is the focal hyperplastic one, seen only close to term and shortly thereafter. In this respect the change is comparable to the hyperplastic change in the breast, which, Fraenkel and Papanicolaou [1] pointed out, does not occur in the premature infant. It may be that hormonal factors similar to those responsible for the stimulation of the mammary gland in the newborn infant are responsible for the histologically similar changes in the prostate. The histologic similarity of these two processes was first pointed out by Schlachta.[10] Halban [30] reexamined Schlachta's material in order to find substantiation for his theory that fetal tissues and organs should evince changes comparable to those seen in maternal tissues and organs during pregnancy. He concluded that the focal areas of columnar, obviously secreting epithelium in the prostate, similar to the changes seen in the fetal mammary glands, were due to maternal stimulation. He made no mention of the squamous metaplasia described by Schlachta [10] and ascribed by the latter to the action of physiologic factors disappearing after parturition. Similarly, Lüttge and von Mertz,[31] in their study of fetal-maternal interrelations, omitted any reference to squamous metaplasia, though they discussed the hyperplastic change in the epithelium of the prostate. Neumann [32] confirmed Halban's [30] observations and subscribed to his interpretation, merely amplifying the conclusions in the light of more recent knowledge and theory concerning the action of maternal hormones. Philipp,[33] in a recent study of changes in the newborn infant resembling those in maternal organs during pregnancy, also made no reference to the squamous change in the epithelium of the prostate.

SUMMARY

All fetuses 23 cm. in crown-heel length and larger, up to term, show squamous metaplasia of the epithelium of the prostate glands and ducts, prostatic utricle and prostatic urethra. The change is seen earliest in the utricle and latest in the prostatic urethra. In both the premature

30. Halban, J.: Ztschr. f. Gerburtsh. u. Gynäk. **53**:191, 1904.
31. Lüttge and von Mertz: Arch. f. Gynäk. **124**:279, 1925.
32. Neumann, H. O.: Ztschr. f. Geburtsh. u. Gynäk. **99**:100, 1930.
33. Philipp, E.: Klin. Wchnschr. **17**:797, 1938.

and the full term infant there occurs several days after delivery a regression of the metaplastic change, traces of which, however, can still be found at 2 months.

The metaplastic change indicates the action of estrogenic substances derived by the way of the umbilical circulation. The epithelial structures of the male acted on are those which, at least in part, are homologues of the vagina.

In infants at term there occurs, in addition, focal hyperplasia of the prostatic epithelium, similar to that seen in the breast of the full term infant, and possibly explained by similar factors.

PATHOLOGY OF SPONTANEOUS PNEUMONITIS AND HEPATITIS IN MICE

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CHICAGO

Considerable work on the viruses is being carried on in mice, much of it by intranasal inoculation. Several spontaneous infections have been encountered in mice.[1] Fortunately, all the infectious agents except one [1g] can be identified immunologically by the use of specific antiserums and the use of surviving immune test animals. Gordon, Freeman and Clampit [1g] described a spontaneous mouse infection against which it was not possible to produce efficacious antiserum in rabbits. Dochez, Mills and Kneeland [1b] previously reported a disease in mice that appears to be identical with it.

Two other virus infections can be passed only by the respiratory route. These are influenza [2] and the pneumonitis of mice described by Horsfall.[1b] However, antiserum protects mice against these infections. It is therefore expedient to describe the pathologic picture of the spontaneous pneumonitis and hepatitis of mice [1g] as an aid in differentiating this disease from other virus infections. Since mice are used commonly in studying the important etiologic agent of influenza, a comparative pathologic study is included here.

METHOD

Mice were inoculated intranasally with 10 per cent emulsions of infected lungs. The emulsions used gave no growth on aerobic and anaerobic culture. Inoculated animals were killed at intervals of twenty-four hours, forty-eight hours and six days. Mice from a stock which was said to be free from spontaneous disease were inoculated with a human strain of influenza virus. These mice were killed six days after inoculation. All tissues were fixed immediately after autopsy.

Department of Medicine, University of Chicago.

1. (*a*) Marchal, J.: J. Path. & Bact. **33**:713, 1930. (*b*) Dochez, A. R.; Mills, K. C., and Mulliken, B.: Proc. Soc. Exper. Biol. & Med. **36**:683, 1937. (*c*) Traub, E.: J. Exper. Med. **63**:533, 1936. (*d*) Nelson, J. B.: ibid. **65**:833, 1937. (*e*) Theiler, M.: ibid. **65**:705, 1937. (*f*) Francis, T., Jr., and Magill, T. P.: ibid. **68**:147, 1938. (*g*) Gordon, F. B.; Freeman, G., and Clampit, J. M.: Proc. Soc. Exper. Biol. & Med. **39**:450, 1938. (*h*) Sabin, A. B.: Science **90**: 18, 1939. (*i*) Horsfall, F. L., Jr., and Hahn, R. G.: Proc. Soc. Exper. Biol. & Med. **40**:684, 1939.

2. Andrews, C. H.; Laidlaw, P. P., and Smith, W.: Lancet **2**:859, 1934.

3. Footnote has been deleted.

Microscopic sections were prepared and stained with hematoxylin and eosin and Mann's stain. Lungs, livers, spleens, pancreases and kidneys were examined. Uninoculated stock mice were similarly studied.

RESULTS

Gross changes were apparent only in the lungs. The livers, spleens, pancreases and kidneys appeared normal. No pleural or peritoneal

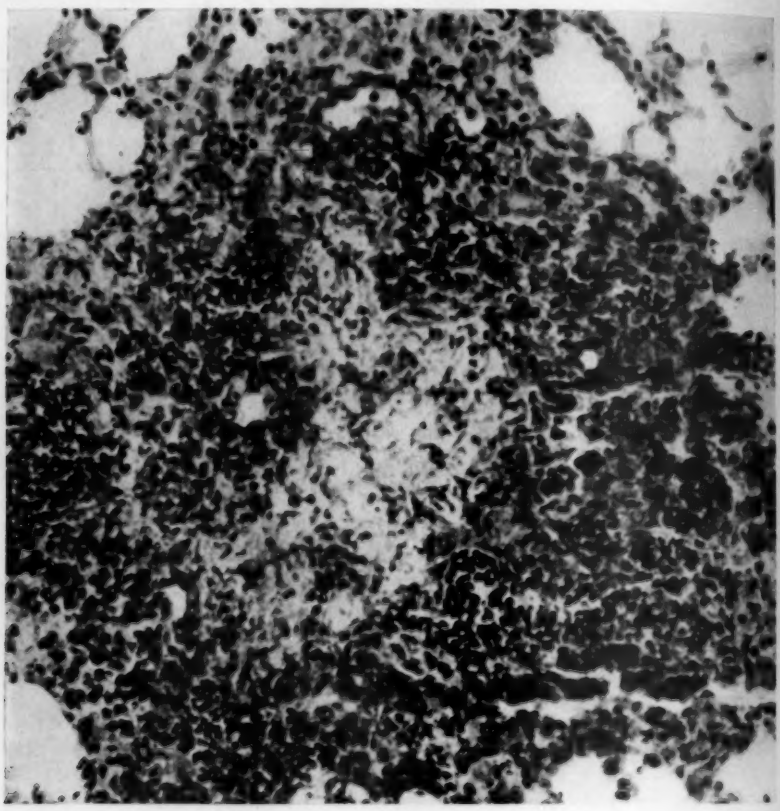

Fig. 1.—Typical area of pneumonitis with central zone of pale bloated cells and fragmented nuclei. Hematoxylin and eosin; × 350.

exudates were seen. Obviously infected lungs had discrete patches of grayish red parenchyma that could be seen through the visceral pleurae of the uncut lungs. These areas stood out against the salmon pink color of the normal lung. The early lesions usually were scattered and appeared commonly in the upper lobes first. As the lesions grew larger they coalesced and became lobar in distribution. Completely consolidated lobes or lungs were voluminous and dark red. The pneumonia

usually spread from the posterior aspect anteriorly. Emphysematous blebs were found frequently in uninvolved portions of the lungs when the infection was widespread. Bronchial exudate was uncommon. The gross picture was not different from that caused by influenza virus in mice.

Straub [4] has given an adequate description of the microscopic picture of the lungs in mice infected with influenza virus. The pneumonitis

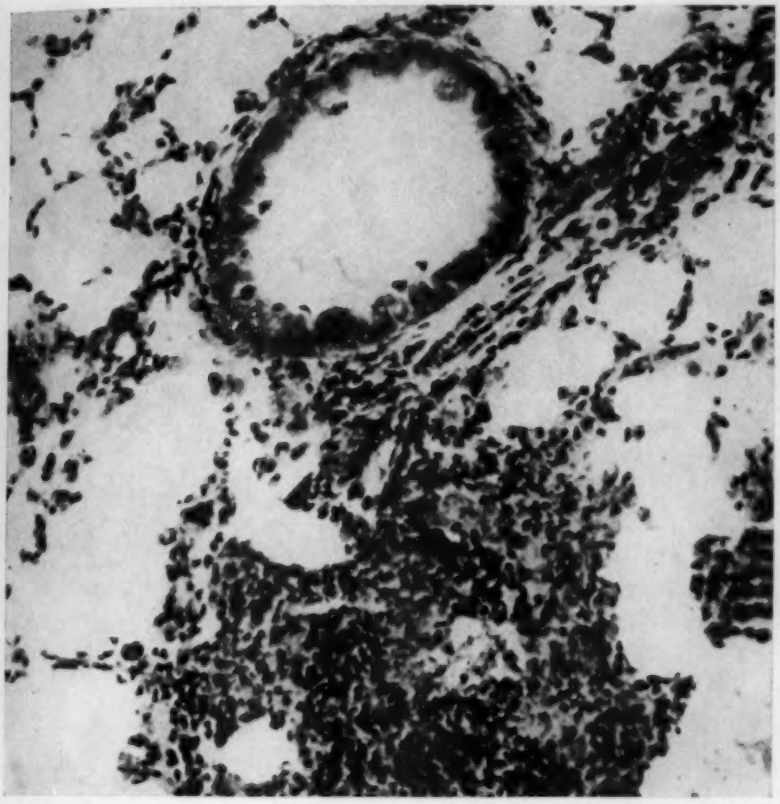

Fig. 2.—Characteristic normal bronchial epithelium of a mouse with spontaneous pneumonitis. Hematoxylin and eosin; × 350.

in the spontaneous infection under study was essentially focal and interstitial, but there was enough intra-alveolar exudate to give the involved portions a homogeneous appearance. The vascular engorgement and tendency toward hemorrhage were not so pronounced as in influenza. Many of the larger lesions had characteristic centers that

4. Straub, M.: J. Path. & Bact. **45**:75, 1937.

were light in staining qualities (fig. 1). These centers consisted of large mononuclear cells with relatively large amounts of cytoplasm. The nuclei in these cells were often ruptured, and nuclear fragments were scattered about in the cytoplasms. The outstanding difference between the two kinds of pneumonia lies in the response of the bronchiolar epithelium to the respective infections. At no stage during the spontaneous infection did the bronchial tree lose or have its epithelium modified

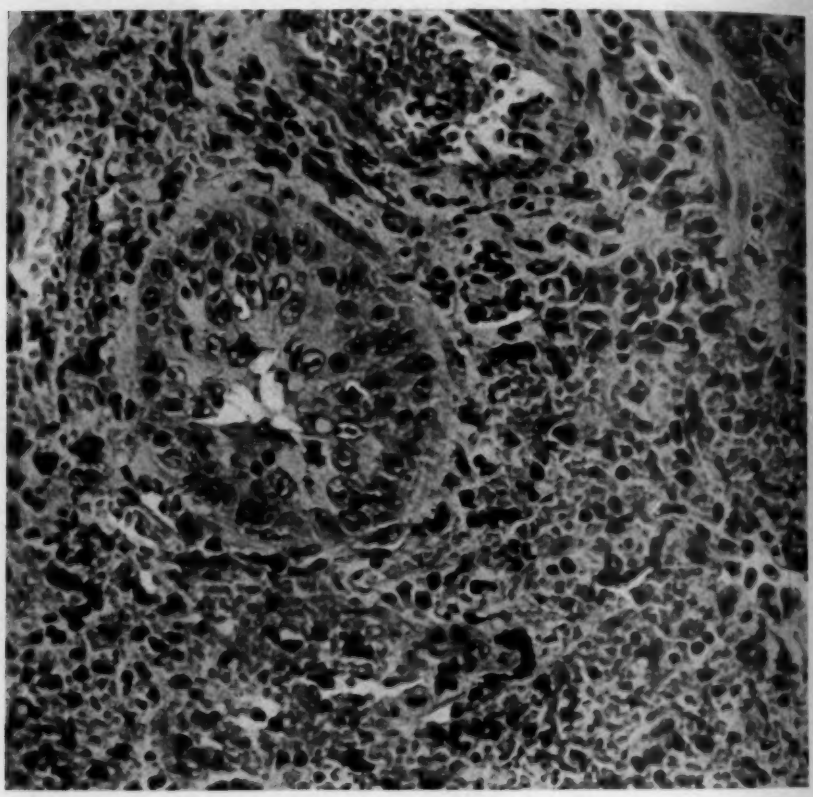

Fig. 3.—Pneumonia caused by influenza virus. Note marked metaplasia of the bronchial epithelium occurring six days after intranasal inoculation. Hematoxylin and eosin; × 450.

(fig. 2). According to Straub, the epithelium in influenza sloughs off and later is replaced by a metaplastic epithelium which is no longer columnar but instead is heaped up in irregular layers. Although this appears to be generally true (fig. 3), it seems likely from the influenza material studied here that metaplasia can proceed immediately without previous sloughing.

The contrast between the livers of mice with the respective diseases was striking. Mice inoculated intranasally with the spontaneous mouse virus often died with severe pneumonia and showed no changes in the liver. However, almost all mice that survived six days had changes in the liver even though the pneumonia was not so extensive as in those that died earlier. The disease was manifested by bloating, paleness and vacuolation of focal groups of hepatic cells (fig. 4). Sometimes the

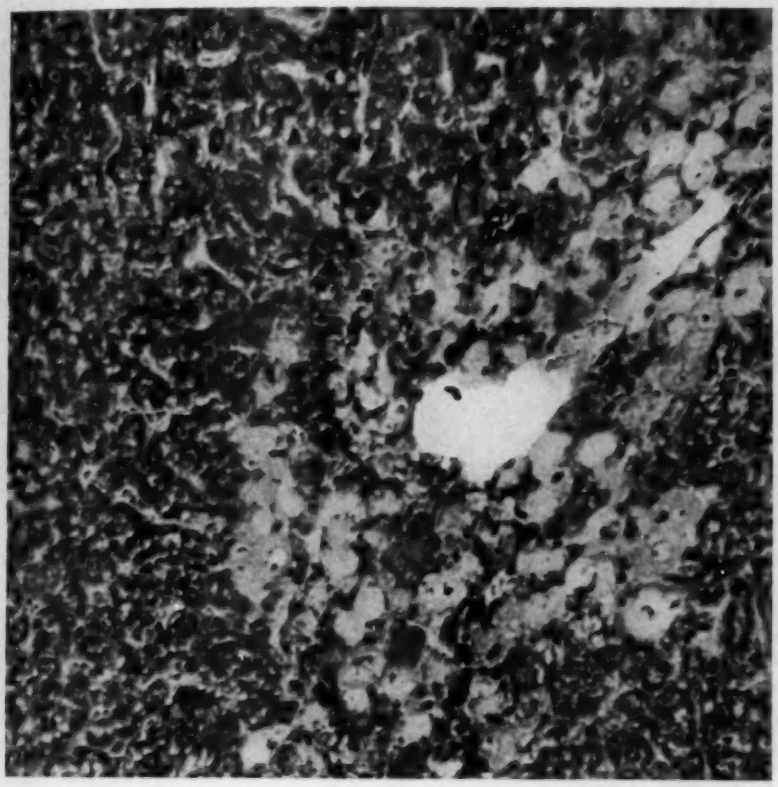

Fig. 4.—Typical lesion of liver in spontaneous mouse infection, six days after intranasal inoculation. Hematoxylin and eosin; × 350.

cytoplasms lost their staining property and left the nuclei in bold relief. In several instances the nuclei of involved cells were ruptured.

None of the mice with influenza showed changes in the hepatic cells of the liver. In 1 instance there was a sparse infiltration by mononuclear leukocytes along the sinusoids, together with hypertrophy of the reticulo-endothelial cells. No inclusion bodies were seen.

COMMENT

The study of viruses is often hampered by an unanticipated encounter with a complicating agent of disease that inhabits mice. At least seven virus infections have been discovered in stock animals during the past two years. This hazard is particularly likely to spoil experimental work when mice are obtained from sources that are not under laboratory control. It appears important to establish means of differentiating these several spontaneous mouse infections and to be able to tell them apart from the conditions caused by viruses that have been adapted to mice. When immunologic methods are inadequate, as in this case, the differential pathologic changes need to be stressed.

SUMMARY

Pathologically, the disease known as spontaneous pneumonitis and hepatitis of mice is characterized by focal and confluent areas of interstitial exudative inflammatory reaction in the lungs, which often contain large pale-staining central zones, and by focal bloating and vacuolation of the hepatic cells. The chief differential points in regard to influenzal pneumonia in mice are the absence of bronchiolar metaplasia and the involvement of the liver.

CYSTITIS FOLLICULARIS IN A DOG

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AND
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Cystitis follicularis is a rare condition characterized by the presence of true lymph follicles in the mucosa and submucosa of the urinary bladder. At times the renal pelvis and ureter may show similar involvement, and the disease is then designated as pyeloureteritis follicularis. The distinctive feature of this condition from the standpoint of pathology is the presence of sharply circumscribed lymph follicles containing germinal centers and differing in no wise from the solitary follicles of Peyer's patches.

In the earlier literature on this subject the term "pyelitis granulosa" was applied to this condition. Von Frisch [1] reported 3 cases of pyelitis granulosa in 1909 and described the condition as follows:

> The mucosa of the pelvis contains numerous millet-sized nodules which are made more prominent by a red zone about the circumference (of the nodule). The red zone consists of extravasation from the capillaries. Microscopically the mucosa is infiltrated with round cells which, close to the surface, group themselves into lymph follicles similar to the solitary follicles of the bowel. The nodules contain a germinal center.

To this picture present day writers have applied the term "pyelitis follicularis" or "cystitis follicularis." The term "pyelitis granulosa" has been retained, however, and Paschkis [2] was the first to distinguish between the two conditions. Whereas in pyelitis follicularis there are present actual lymph follicles with their specific characteristics, such as germinal centers, in pyelitis granulosa one finds merely unorganized collections of lymphocytes, usually of inflammatory origin.

CAUSES

Our chief interest in this subject, and the purpose of this report, lies in the etiologic explanation of cystitis follicularis. Four causative factors are mentioned in the literature; these are gonorrhea, syphilis, typhoid fever and tuberculosis. Von Frisch, in reporting 3 cases, stated

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From the Division of Experimental Medicine, the Mayo Foundation.

1. von Frisch, A.: Verhandl. d. deutsch. Gesellsch. f. Urol. **2**:270, 1909.
2. Paschkis, R.: Folia urol. **7**:55, 1912.

that gonorrheal infection may be the etiologic factor. Loewenhardt [3] reported a case of pyelitis follicularis and discussed at length the possible etiologic relationship between this disease and syphilis. Baetzner [4] expressed the belief that typhoid fever bears a causal relationship to cystitis follicularis. Tuberculosis was mentioned by Symmers [5] as a possible causal agent. He stated his belief that the follicles are formed as a response of the tissues to a toxic irritant and cited tuberculosis as a good example of toxic lymphoid hyperplasia.

We present a case of cystitis follicularis for the purpose of reexamining the various claims that have been made concerning the causation of this disease.

REPORT OF A CASE

Clinical Findings.—During the course of some experimental work one of us (L. F. G.) had occasion to examine cystoscopically an adult female dog, which was apparently in good health. On examination the trigon and base of the bladder were found to be covered with small, grayish white nodular excrescences, each surrounded by a red peripheral zone. The nodules varied in diameter from 1 to 2 mm. and appeared solid. Several nodules were removed for biopsy, and a diagnosis of cystitis follicularis was made from a study of this tissue. Intravenously administered indigo carmine appeared in good spurts from each ureteral orifice two minutes after injection (normal). No similar condition was found in more than 60 other dogs that were subjected to cystoscopic examination.

Gram's stain applied to the urine revealed an enormous number of gram-negative bacilli; growth on eosin–methylene blue and blood agar revealed a pure culture of Escherichia coli. Urinalysis revealed pus (grade 3 on the basis of grades 0 to 4), an occasional red blood cell, albumin (grade 2) and no casts. The value of urea was 23 mg. in 100 cc. of blood. The red and white cell counts, the hemoglobin content and the differential blood smear were normal. A Ziehl-Neelsen stain of urine from the bladder revealed no acid-fast bacilli.

Necropsy.—The dog was killed and necropsy performed immediately. All of the viscera were carefully examined, but the only gross evidence of disease was in the bladder. The wall of the organ was markedly thickened (0.5 cm.). The mucosal surface was studded with innumerable small glistening ovoid nodular elevations having an average diameter of 0.1 cm. (fig. 1 *A*). Each nodule had a flesh-colored central region and in most instances was surrounded by a narrow but definite peripheral zone of what appeared to be hemorrhage or congestion. For the most part the lesions were definitely discrete. In only a few instances did the nodules appear to be in apposition. In the region of the trigon the nodules were less numerous and were more or less clear or colorless. The peripheral zones of redness did not occur with the nodules in this region. A larger number of the nodules occupied the anterior surface of the organ. No lesions were observed in the urethral or the ureteral mucosa.

Tissues for histologic examination were obtained from the bladder, kidneys, liver and spleen.

Microscopic Examination.—(*a*) Bladder: The mucosa of the bladder, instead of being in a continuous plane, showed many cleftlike depressions, produced by

3. Loewenhardt, F.: Arch. f. Dermat. u. Syph. **84**:395, 1907.
4. Baetzner, W.: Ztschr. f. urol. Chir. **1**:285, 1913.
5. Symmers, D.: Arch. Int. Med. **21**:236, 1918.

the mucous layer dipping into the stroma. The transitional character of the epithelium was evident and the cuboid cells in contact with the basement membrane were easily recognized. Scattered promiscuously throughout the stroma were large nodular deposits of basophilic cells that were definitely of a lymphoid character (fig. 1*B*). The majority of the lymphoid nodules had a striking resemblance to the lymph nodules of normal lymph nodes. A central region

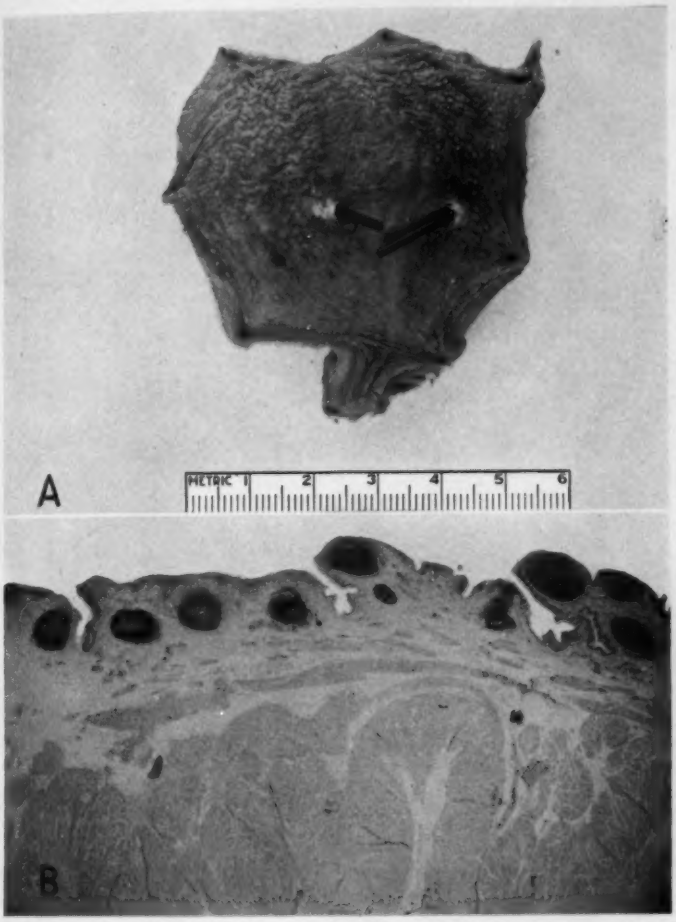

Fig. 1.—Cystitis follicularis. *A*, photograph of a gross specimen showing numerous small discrete nodular elevations in the mucosa. *B*, photomicrograph showing the numerous lymphoid nodules under the mucous layer; × 10.

similar to the germinal center was observed in many of the structures. Here the cells were less basophilic and more loosely arranged. Some of the cells in the central regions showed hyperchromatic nuclei, but definite mitosis was not observed. The nodules failed to show peripheral encapsulation, nor were there other signs of a reactive process in the outer zones of the lymphoid structures. The lymphoid

cells seemed to merge in an indefinite manner with the connective tissue of the stroma. The blood channels of the stroma were prominent, owing perhaps to the state of congestion. Extravascular blood indicative of hemorrhage was readily

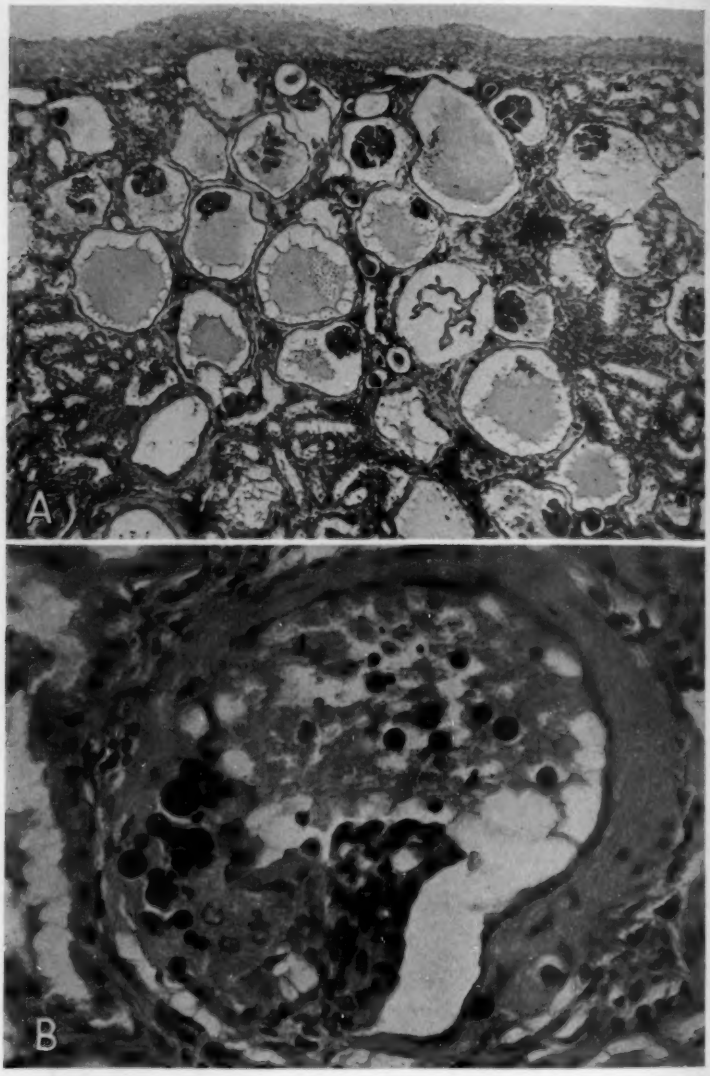

Fig. 2.—*A*, portion of the cortex of the kidney characterized by marked dilatation of Bowman's capsule and atrophy of the glomerular tufts; × 60. *B*, marked thickening of Bowman's capsule with atrophy of the glomerular tuft and occurrence of calcium; × 480.

demonstrable. The regions of hemorrhage were most noticeable in the uppermost portions of the stroma. Considerable numbers of diffusely arranged lymphoid cells occurred in the stroma in the zone adjacent to the basement membrane.

Although the epithelial layer was intact throughout most of the surface, there were regions where the epithelial cells had been denuded. This situation obtained most frequently where the lymphoid nodules had occurred in the upper portion of the stroma and had expanded peripherally and bulged upward into the basement membrane. In these circumstances opportunities for hemorrhage into the bladder were evident.

(*b*) Kidneys: Both kidneys were seriously compromised by extensive morbid changes that extended from the renal pelvis to the outermost region of the cortex. In the pelvis the connective tissue of the stroma was the site of considerable numbers of histiocytes and lymphocytes. Polymorphonuclear leukocytes or other signs of an acute process were absent. Severe fibrotic changes had occurred throughout the medulla, where large numbers of the tubules had been replaced by connective tissue which was becoming hyalinized. The epithelium in the tubules that remained was greatly flattened, and many of the lumens contained hyaline casts.

In the cortex, although there were large numbers of morphologically adequate glomeruli, there occurred throughout the cortex many affected renal corpuscles. These were characterized by extreme dilatation of Bowman's capsule and subsequent atrophy of the glomerular tuft (fig. 2*A*). Although in most instances the space resulting from the dilatation of Bowman's capsule was filled with a clear homogeneous substance, in a few there were seen unstained and unidentified cell-like forms and deposits of calcium (fig. 2*B*). In numerous instances the stroma of Bowman's capsule was markedly thickened and a few epithelial crescents were noted. In many instances the entire renal corpuscle had been replaced by a dense hyalinized substance. While this substance resembled amyloid, amyloid could not be demonstrated in sections stained with congo red.

(*c*) Liver and Spleen: There were no significant changes in these tissues.

Summary of Pathologic Changes.—The recognizable pathologic changes were limited to the bladder and the kidneys. The lesions of the bladder were classic examples of the entity designated as cystitis follicularis. Both kidneys were the site of severe changes indicative of a morbid process of considerable duration. There was marked fibrosis of large regions of the medulla, and there were striking changes in many of the renal corpuscles. These included dilatation of the glomerular spaces, atrophy of the glomerular tufts and extreme thickening of Bowman's capsule.

COMMENT

Clinically, cystitis follicularis is perhaps of more importance to the urologist concerned with human beings than to the veterinarian. It is without question an extremely rare condition in dogs. The disease has not heretofore been observed among the large number of dogs examined at necropsy here, and in standard texts of animal pathology the condition is either not mentioned or dismissed with a brief paragraph.

There is no convincing evidence that any of the etiologic agents advanced bear more than an incidental relationship to cystitis follicularis. In studying the different case reports it becomes obvious that the reasoning employed is chiefly of the post hoc, ergo propter hoc variety. Syphilis, gonorrhea and typhoid fever are not known to occur in the dog; hence none of these diseases can be the etiologic factor in the case

which we report. Although tuberculosis occurs in the dog, its occurrence is exceedingly rare, and there were no evidences of its presence in this case.

In reviewing all the literature on pyelitis and cystitis follicularis which we were able to obtain, the association of this disease with Esch. coli has been striking. Of 20 reported cases, Esch. coli was found in 11; in 3 cases the urine was reported negative for bacteria, and in the remaining 6 cases no mention was made of a bacteriologic study. That infection with Esch. coli alone is not the causative factor is indicated by the relative frequency of this type of infection as compared with the infrequency of this disease.

In the case which we have reported the morbid changes in the kidneys are perhaps of more interest to the pathologist than are the conditions in the bladder. The kidneys presented lesions the genesis of which is not clear. The signs of chronic pyelonephritis and the marked fibrosis of the medulla suggest a previous infection; yet the absence of residual evidence of a previous infection in the outer zone of the cortex makes this explanation difficult to sustain. It is true that many glomeruli showed definite signs of disease, but the surrounding tubular structures were normal. The cystic dilatations of the glomerular spaces could conceivably have resulted as a consequence of the elimination of so many of the tubules by the connective tissue changes in the medulla. If the egress of the urine from the tubular system was interfered with or stopped and the glomeruli continued to function, filling of the glomerular spaces would occur. Another possibility that might be considered in explaining the occurrence of the dilated glomerular spaces is a congenital tendency toward polycystic kidney. This does not seem tenable and is hardly worthy of further comment.

There is no direct evidence that the cystitis follicularis was related etiologically to the pathologic changes in the kidney.

SUMMARY

Cystitis follicularis in an adult female dog is described. The cause is obscure; the various etiologic factors usually ascribed to this disease cannot pertain to the case which we report. Both kidneys were the sites of extensive fibrotic changes, which were probably unrelated to the lesions in the bladder.

Case Reports

HEMANGIOENDOTHELIOMA OF THE LUNG

Report of Two Cases

ALFRED PLAUT, M.D., NEW YORK

True angioendothelioma is rare; in the lung it is extremely rare.[1] Two cases have come under observation lately and are described here. One case, in which the small single tumor was a minor accidental finding, will be mentioned but briefly. The other touches on problems of general pathology and thus merits a more detailed study.

CASE 1

A 35 year old white housewife was admitted to Beth Israel Hospital acutely ill with the symptoms of meningitis. Seven hours after admission she became comatose; she died in coma three hours later. Thus, not much attention could be given to her circulatory system; the clubbed fingers, however, were noted, as well as a prolonged systolic blow at the apex of the heart. The patient was known to have had heart disease since the third year of life, and she had been forbidden to have children on account of this. There were no pulmonary symptoms during her short stay in the hospital.

At autopsy the outer appearance of the body was not remarkable except for the slight clubbing of the finger tips and some cyanosis of the nail beds.

The heart was not enlarged (325 Gm.). The valves, notably the tricuspid and the mitral, gave the gross and the microscopic picture of healed endocarditis. The tricuspid valve appeared insufficient; the wall of the right ventricle was thick (0.7 cm.); the wall of the left ventricle was not thickened (1 cm.). A defect 2 cm. in diameter was situated in the uppermost portion of the interventricular septum.

The gross aspect of the lungs was not remarkable.

On microscopic examination the lung tissue proper exhibited only severe widespread congestion and moderate patchy edema. The media in the pulmonary artery and its large branches, notably in the neighborhood of thick atheromatous patches, was more severely destroyed than is customarily seen in atherosclerosis. There was no evidence of a syphilitic lesion. Inflammation was entirely absent (fig. 1 *A*).

Many arterial branches were thick walled; they were excessively tortuous, and the tortuosities were irregular. Muscle and elastic tissue were not regularly arranged; the latter irregularity had nothing to do with atherosclerosis. The vessels had saclike, partly loculated attachments. The wall of each diverticulum-like sac consisted of vessel wall but not of the entire vessel wall. These walls were thinner than the original wall of the vessel, and their elastic lamellae were irregularly distributed. There was no inflammation (fig. 1 *B*). In some places the

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1. Other organs which, like the lung, consist of blood vessels to a large extent seldom produce tumors (spleen, placenta). Among these rare tumors, however, tumors of the blood vessels predominate.

EXPLANATION OF FIGURE 1

A, the main branch of the pulmonary artery (case 1) under low magnification. Note the atherosclerosis and the unusually severe destruction of the media (There is perhaps a constitutional weakness of the wall.)

B, a blood-filled aneurysm-like pouch protruding from the outer layers of the artery (case 1). It is partly subdivided by spurs, which contain elastic tissue (upper part).

C, a not entirely normal artery giving off a branch which after a short course becomes distended with angioendothelioma (case 1). In the tumorous region the elastic lamellae are destroyed. They become distinct again in the further course of the vessel.

D, a thin-walled, wide, branching vessel with angioendothelioma (case 1). In this and subsequent figures, the slides shown in which elastic lamellae appear were stained with Weigert's stain and lithium carmine; the others, with hematoxylin and eosin.

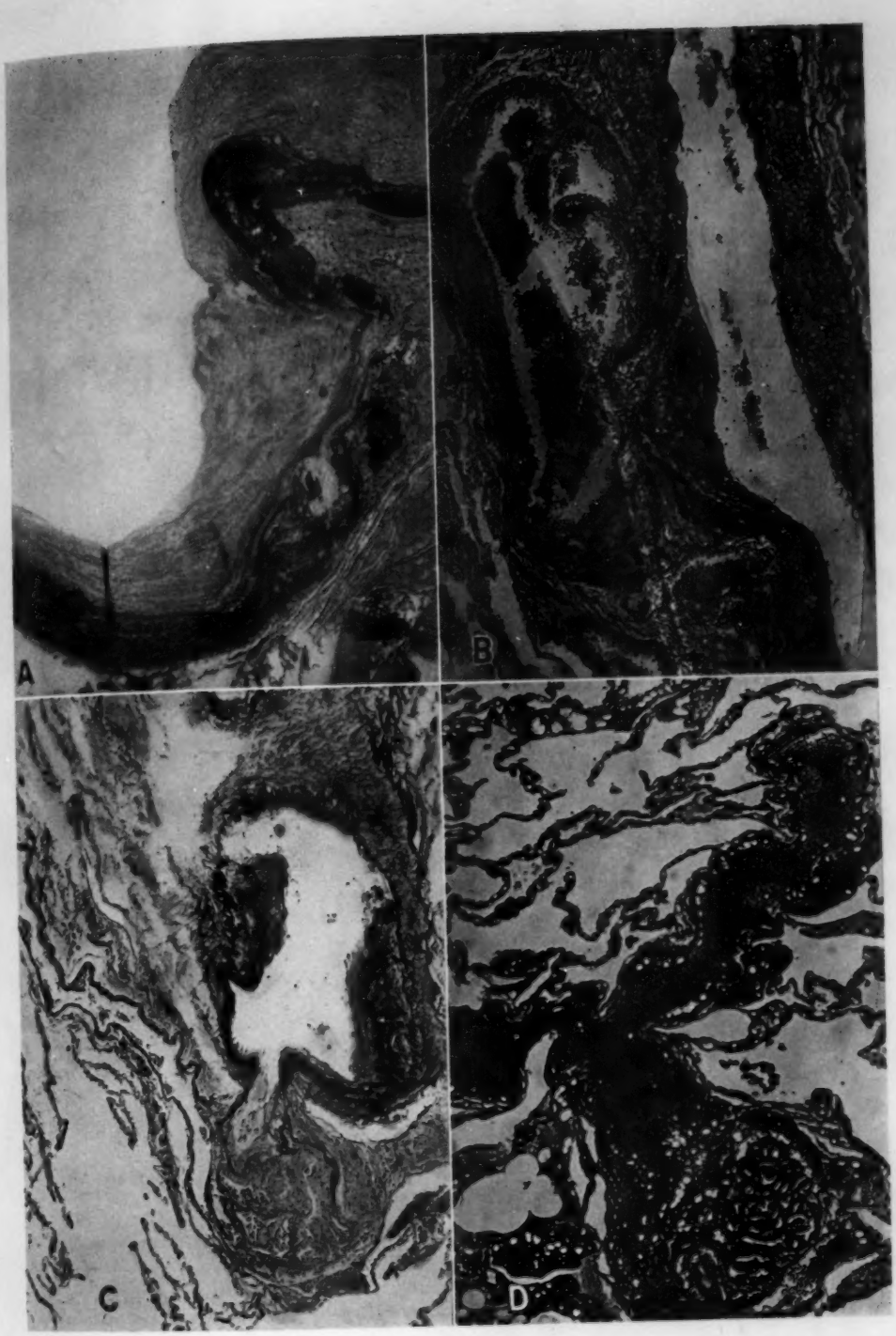

Figure 1

EXPLANATION OF FIGURE 2

A, loculated intravascular angioendothelioma (case 1). Note (here and in all the figures) the complete absence of thrombosis.

B, endothelioma filling part of a distended vessel (case 1). It contains elastic fibers. Note near the upper edge a portion of a normal artery.

C, small intravascular hemangioendothelioma (case 1).

D, blood-filled spaces within a thick arterial wall (case 1). Note the cellular overgrowth.

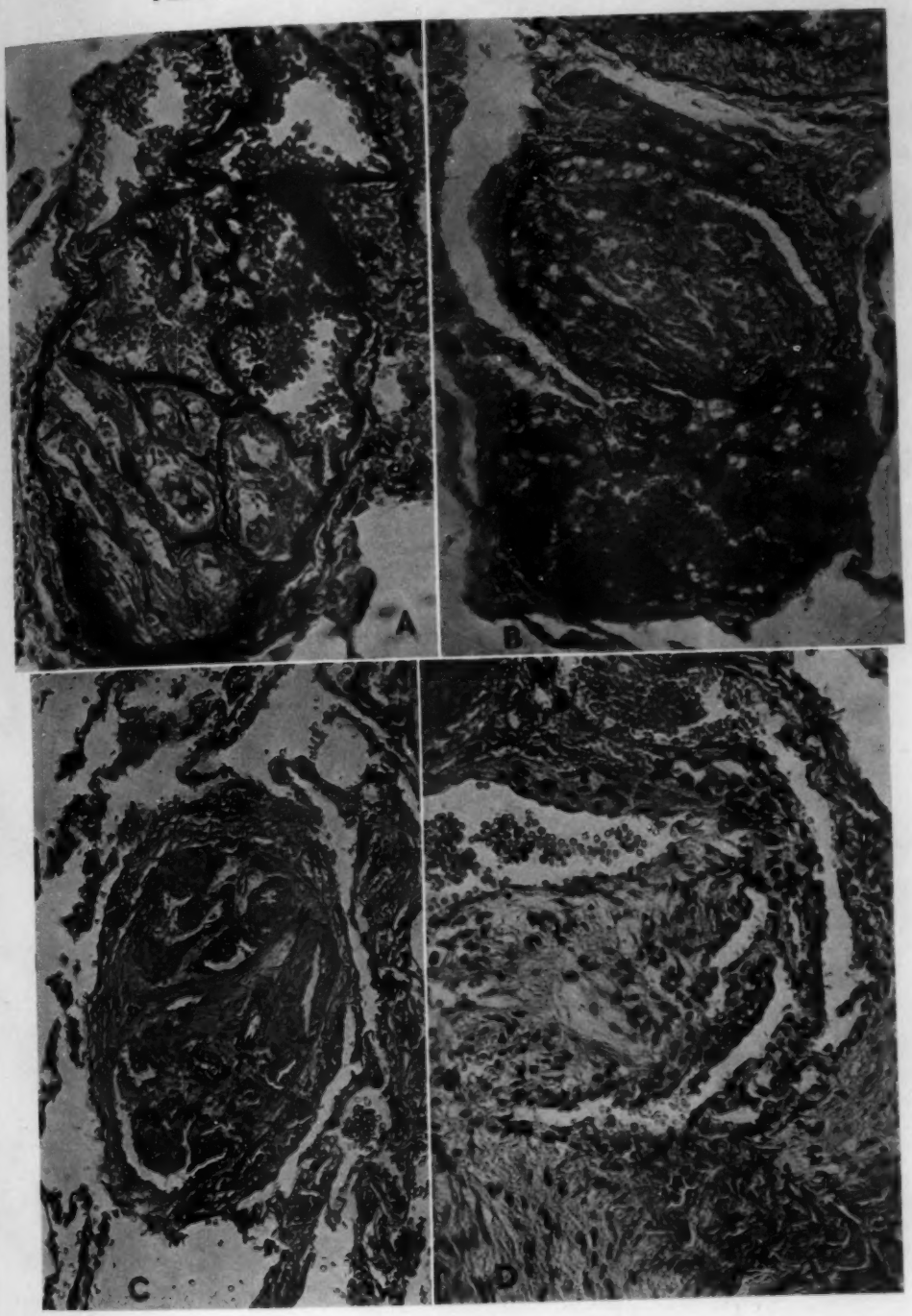

Figure 2

EXPLANATION OF FIGURE 3

A, intravascular angioendothelioma, precapillary type (case 1) (higher magnification of figure 1 *D*).

B, capillary angioma (case 1). This tumor is diffuse and not intravascular. The picture is the same as that described by de Lange and de Vries Robles.

C, small endothelioma of the lung (case 2) under low magnification.

D, endothelioma in continuity with capillaries (case 2).

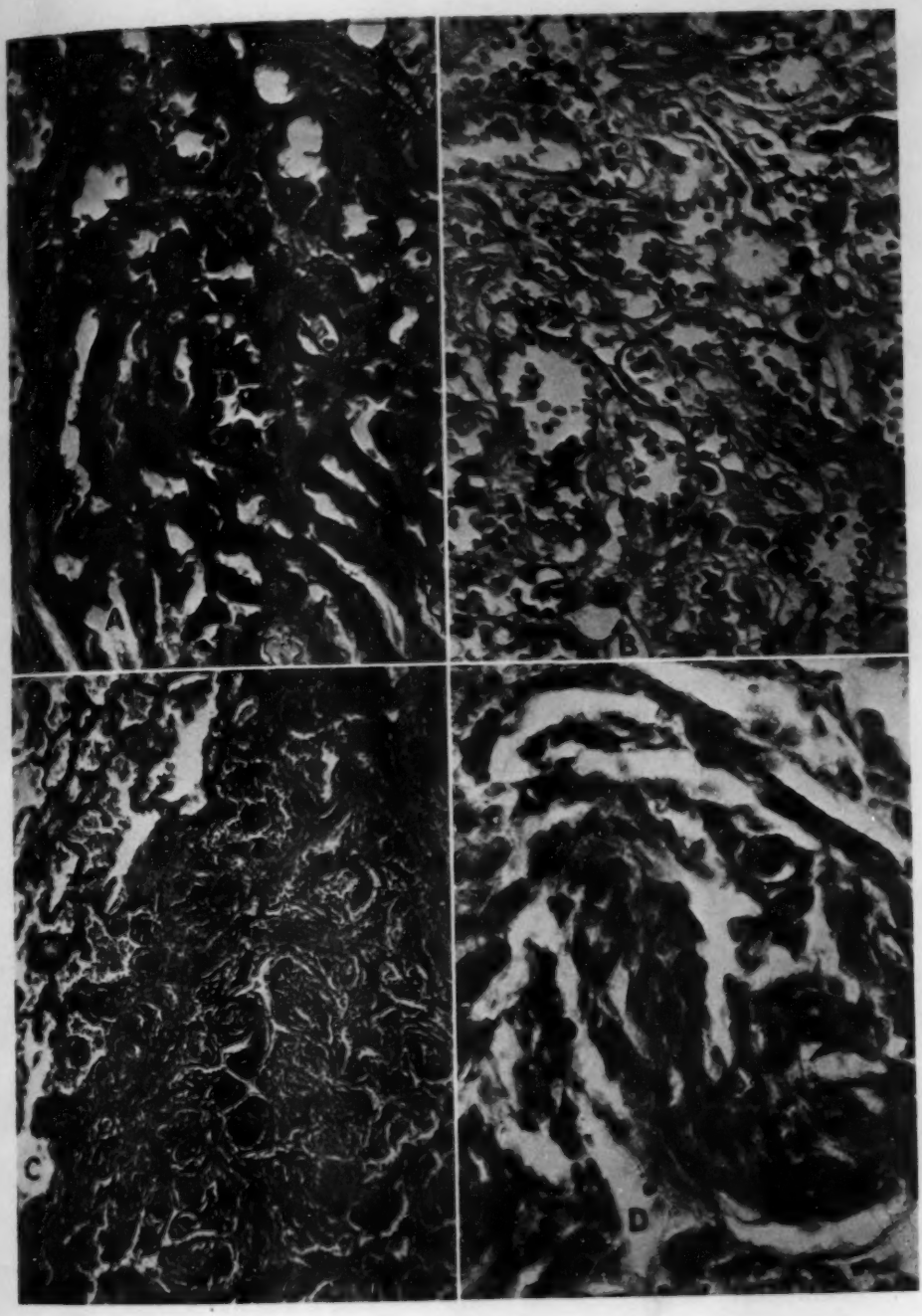

Figure 3

lumens of these pouches were incompletely subdivided by protruding ridges or spurs, which contained elastic lamellae (fig. 1 *B*).

The thick walls of these irregular arteries showed clefts and cavities occupying all layers. The shape of the cavities was much more irregular than that of the ellipsoid sacs. On serial sections these cavities were found in direct communication with the lumens of the arteries. Since most of the clefts and cavities contained numerous red blood cells, it was assumed that they all either were communicating with the lumens of the vessels or at least had been communicating with them (fig. 2 *D*).

The most widespread and most striking abnormality of vessels in this lung was represented by numerous very thin-walled, very wide, mostly blood-filled vessels. In spite of the fact that these vessels sprang from rather large arteries which were provided with a thick media, their walls consisted of nothing but the endothelium and a compact elastic layer (fig. 1 *C* and *D*).

All of the three mentioned abnormal vessel formations were the seat of small angioendotheliomas. The structure of the tumors varied. Areas of endothelial overgrowth in the walls of complicated labyrinths of blood spaces left the observer in doubt as to their blastomatous or hypertrophic character (as far as such a distinction still has a meaning) (fig. 2 *D*). Such "beginning endotheliomas," as well as definite ones, frequently were situated in the outer layers of thick-walled abnormal arteries, but they were seen also at the point where one of the intramural blood spaces communicated with the lumen of the artery.

Other tumors were situated in the lumens of wide, thin-walled vessels. In some instances (figs. 1 *C* and 2 *A* and *B*) one gained the impression that the distention of the vessel might have been caused to a certain extent by the tumor; in others (fig. 1 *D*, for instance) the angioendothelioma seemed to be situated somewhere within a system of distended vessels. Angiomatous structures prevailed in some tumors (figs. 1 *D*, 2 *A* and 3 *A*) and endotheliomatous in others (fig. 2 *B*). They appeared mingled in some intravascular nodules (fig. 2 *C*). But the elastic tissue stain revealed elastic fibers even in solid endothelial masses, denoting an angiomatous component (fig. 2 *B*). Sometimes parallel elastic lamellae were separated by single rows of endothelial cells; sometimes only fragments of elastic tissue were found.

In one section a subpleural area, measuring 1 by 0.3 cm., was occupied by a capillary angioma (fig. 3 *B*). It consisted of a labyrinth of mostly narrow, partly wide capillaries, all of which were more or less filled with well preserved erythrocytes. The capillary walls were thin; the endothelial nuclei were large and numerous. Some capillaries were very wide and were distended by partly conglutinated red cells. At some points the arrangement of the capillaries reminded one of the architecture of the alveolar walls. The angioma was not sharply separated from the surrounding lung tissue. No continuity with one of the hemangioendotheliomatous nodules could be established.

This was the only capillary angioma in the many sections examined. Occasionally in other sections compressed lung tissue was seen in which the capillaries were the dominant feature. There was, however, no tumorous overgrowth in these areas.

As mentioned, only one area of capillary angioma was found. The other tumors were present in almost every section; they were found near the pleura and near the hilus. (Sections were taken from all the lobes.)

There were no abnormalities of blood vessels in the other organs.

CASE 2

Another endothelioma of lung was found accidentally on microscopic examination. A 53 year old woman had died of heart disease. At autopsy mitral stenosis was found, also an organic insufficiency of the tricuspid valve caused by old rheumatic endocarditis of the valve. In the stained paraffin section the tumor appeared to the naked eye as a bluish triangular subpleural field, the sides of the triangle measuring 3 mm., 3 mm. and 2 mm. It was incompletely separated from the surrounding lung tissue by several layers of connective tissue. The surrounding lung tissue was normal except for stasis and the presence of heart failure cells. In this triangular field the alveolar structure was essentially preserved. The spaces, however, were occupied by characteristic whorls of endothelioma. Many blood-filled capillary spaces were situated within the tumor (fig. 3 *C* and 3 *D*).

REVIEW OF THE LITERATURE

Textbooks hardly mention angioma or endothelioma of the lungs. Only Roussy and Leroux [2] have mentioned angioma of the lung. Dr. Roussy informs me that in the postmortem material in Paris angioma of the lung has been observed once, some time ago. No further data concerning this case are available, and no other case of a tumor of the blood vessels in the lung has been encountered since in Paris. The loose application of the term "endothelioma" for decades past makes study of the pertinent literature a tedious and thankless task. None of the reports found is really a report of a case similar to case 1; no multiple intravascular pulmonary hemangioendothelioma has been described, to my knowledge. Cases have been described, however, which have important points in common with the ones reported here.

De Lange and de Vries Robles [3] observed multiple capillary angioma in the lung of a 2½ month old girl. The clinical symptoms had been inconclusive. The infant died in convulsions, without fever. At autopsy two bulging areas, each 1.5 cm. in diameter, were noted on the upper lobe of the left lung and one twice as large on the upper lobe of the right lung. Microscopically there was massive new formation of small and very small capillaries; a few of the endothelial cells contained mitotic figures. Dr. de Lange has let me have a piece of this lung specimen. I thus can state that the capillary angioma observed in Amsterdam is identical with that observed by me. The diffuse capillary angioma in my case, however, occupied only a small area, while that observed by de Lange constituted the whole of a large pulmonary lesion.

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2. Roussy, G., and Leroux, R.: Diagnostic des tumeurs, Paris, Masson & Cie, 1921, p. 45.

3. de Lange, C., and de Vries Robles, S. B.: Ztschr. f. Kinderh. **34**:304, 1922.

A similar picture of capillary angioma is given in a paper by Wollstein.[4] The patient was a girl 4 months old, who died on the day after admission to the hospital. At autopsy the diagnosis was malignant hemangioma of the lung with multiple visceral foci. Many organs and tissues were affected. The lung was considered the organ undoubtedly most involved, and the lesion was named accordingly. Figure 2 in Wollstein's paper shows a lesion similar to the capillary angioma which I have described and to the lesions described by de Lange and de Vries Robles. Otherwise the case is entirely different.

The tumor observed by Hall [5] belongs to the same group of multiple malignant tumors in different organs, the lung probably representing the primary site. Hall's patient was a woman 40 years old; she died with multiple malignant hemangiomas in the lungs, pleura, liver and retroperitoneal lymph nodes. The largest tumor was found in the right lung. The heart was normal except that the opening of the right coronary artery was missing in the usual location. A small right coronary artery was found in the subepicardial fat, about 1 cm. from the aorta. Hall stated that "the presence of congenital anomalies of the circulatory system in this patient may have etiological significance."

Other cases of multiple malignant hemangioma with involvement of the lung will not be discussed here since they are essentially different from the cases reported here. Wollstein's case has been mentioned on account of the histologic similarity and Hall's case because of the combination with a malformation of the heart.

True endothelioma of the lung has been observed by Edwards and Taylor.[6] These authors described 4 large pulmonary tumors, all of which were removed by lobectomy. Their third case is one of an endothelioma with whorl-like arrangement similar to that in the second case recorded in this paper. The patient was a 56 year old woman with clinical and roentgenologic symptoms of a rather large tumor of the lung. I have not been able to form an opinion about the histologic character of the three other pulmonary tumors described by Edwards and Taylor. It therefore seems preferable not to discuss them here. The authors themselves considered it "difficult to be absolutely exact in assessing the nature of these tumors. . . ." Considering the great rarity of benign tumors of pulmonary vessels, two other reports will be mentioned.

Cavernous hemangioma of the type usually found in the liver is rare in the lung. One such tumor has been described by Rodes [7] in a 25 year old man. This patient died of intrathoracic hemorrhage which, as the autopsy showed, had been caused by rupture of the cavernous tumor. The tumor had given a definite circumscribed shadow on the roentgen film, and the patient for years had exhibited symptoms of pulmonary disease. He also had clubbed fingers.

Dr. Rodes and Dr. Peterson gave me the opportunity of studying a section of this lung. The picture of the tumor is that of cavernous

4. Wollstein, M.: Arch. Path. **12**:562, 1931.
5. Hall, E. M.: Am. J. Path. **11**:343, 1935.
6. Edwards, A. T., and Taylor, A. B.: Brit. J. Surg. **25**:487, 1938.
7. Rodes, C. B.: J. A. M. A. **110**:1914, 1938.

hemangioma. There is no overgrowth of endothelium. In the surrounding lung tissue some blood vessels are widely distended and resemble the thin-walled arterial branches observed in the tumor which I have described. Aside from one small glandlike duct, which obviously is not a bronchus, no other structural abnormalities are seen.

From the description given by Rodes and from the material that I could examine myself, no conclusion can be drawn as to the presence or absence of abnormalities in the pulmonary blood vessel system in Rodes's patient.

Obviously similar was the pulmonary lesion studied by Bowers.[8] A newborn boy became extremely dyspneic on the second day after a normal delivery. He died within a few minutes. At autopsy the left pleural cavity was full of blood clots, the heart being shifted to the right. Numerous raised branching bluish areas were found at the base of the right lung. Similar ones were situated in the lower lobe of the left lung. One of these apparently had ruptured. The histologic picture was that of hemangioma.

This is the only hemangioma of the lung Bowers has found in a search of 23,897 autopsy records which contained 64 reports of visceral hemangioma (mostly in the liver). There is no statement as to the presence of other abnormalities in the lung, notably concerning the pulmonary vessels.

Thus the number of cases comparable to those reported here, even in some respects only, is very small (de Lange and de Vries; Wollstein; Hall; Edwards and Taylor [case 3]. The fact that they all concern females is statistically insignificant but worth mentioning. A survey of the literature on metastasizing angioma, multiple angioma and angiomatosis did not reveal a preponderance of one sex.

Attempts to compare case 1 with instances of intravascular endotheliomatous tumors of other organs did not meet with much success either. Benda [9] has seen diffuse angioendothelioma of the kidney. His description suggests a lesion which in some respects is similar to the one I have described; it definitely presents multiple endothelioma within blood vessels—in his case, the renal veins. No photograph is given.

In discussing the anomalies which may be associated with congenital heart disease Maude Abbott did not mention the pulmonary vessels; neither did Schwalbe in his book on malformations.

Finding the small endotheliomatous tumors in distended vessels, I naturally was driven to inquire whether or not distended vessels in other parts of the body are sometimes the seat of endothelial tumors. Ewing [10] mentioned a group of "rare and somewhat obscure intravascular endotheliomas of corpus cavernosum." He quoted Schlagenhaufer as having described such tumors in hemorrhoidal veins. Ewing himself had seen endotheliomatous tumors in thrombosed varicose veins within small, encapsulated, slowly growing subcutaneous tumors.

8. Bowers, W. F.: Nebraska M. J. **21**:55, 1936.

9. Benda, C., in Henke, F., and Lubarsch, O.: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 915.

10. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928, p. 336.

Borst [11] mentioned an endothelioma of the corpus cavernosum of the penis. I have been unable to find photomicrographs of these tumors; thus I cannot say how far they resemble mine histologically. A search of pertinent dermatologic and urologic literature did not yield more information.

No tumor of pulmonary blood vessels, to my knowledge, has been reported in veterinary literature.

COMMENT

Many more questions arise than the scanty material available will permit one to answer or even discuss. There is, first, the problem of pathologic entities. How far do the different forms of tumors of blood vessels in the lung represent different diseases? How far do they belong together? The malignant metastasizing forms, as observed by Hall and by Wollstein, for instance, seem remote from the cavernous tumors described by Rodes and by Bowers. But among the many metastases in Wollstein's case, the one in the adrenal marrow was of the cavernous type, thus indicating a degree of kinship.

Had I not found the single focus of capillary angioma, I should have considered the tumor I have described altogether different from that of de Lange and de Vries Robles. With this capillary angioma present, the two forms of neoplasia of pulmonary blood vessels appear rather closely related. Hall's case with the multiple malignant tumors exhibits a resemblance to my case 1 in the coexistent malformation of the heart.

In considering the genesis of tumors of blood vessels one thinks of the close relation of such tumors to congenital lesions. The tumors discussed here as having some bearing on those presented were observed in a boy 2 days old (Bowers); a man of 25 years (Rodes); a 2½ month old girl (de Lange and de Vries Robles); a 4 month old girl (Wollstein); a woman 40 years of age (Hall); a woman 56 years of age (Edwards and Taylor [case 3]). The fact that 3 tumors were observed in patients in the first year of life cannot be neglected in so small a series.

In my case 1 the connection with malformation is striking. In addition to the defect of the interventricular septum there was an anatomic abnormality in the blood vessels which contained the tumors. There is no doubt in my mind that this abnormality of pulmonary vessels represented a malformation, and it does not seem far fetched to assume a connection between this malformation and the development of the multiple hemangiomas.

Overgrowth within a blood vessel may be caused in part by a circulatory disorder. The circulatory conditions in this lung must have been influenced by many factors. Aside from the large interventricular septal defect there were narrowing and occlusion of some medium and small arteries, destruction of the media in the atheromatous large arterial branches, tortuosity, thickness of wall and pouches as described and finally, a large number of extremely distended thin-walled vessels. No detailed evaluation of these opposing factors can be undertaken. Perhaps the many very wide vessels acted as a pressure chamber for the

11. Borst, M.: Allgemeine Pathologie der malignen Geschwülste, Leipzig, S. Hirzel, 1924, p. 144.

right ventricle; this would explain the relatively slight degree of right ventricular hypertrophy.

In experimental animals, as well as in human beings, slowing up of the arterial circulation can lead to overgrowth of the intima. To my knowledge, no tumor has ever resulted from such overgrowth. In the enormously and abruptly distended, thin-walled, abnormal arterial branches in the lung which I have described there must have been marked local slowing up of the blood stream. These vessels, however, while being arterial branches in the circulatory sense, have little in common with arterial branches anatomically. They do not have a muscle coat worth mentioning. Therefore, the reaction of their wall could not be expected to be similar to the reaction of a wall which is provided with a well developed muscular media. How far the slowing up and the eddy formation were factors in the development of the intravascular tumors is unknown. Severe chronic stasis in the lung is so frequent in acquired and in congenital disease that its presence in both cases reported may as well be accidental.

The complete absence of thrombosis is astonishing in the presence of so much distention of large and small vessels and so many points of sudden changes in width. Not even in the arteries which are narrowed by overgrowth of the intima is there any trace of recent or old thrombosis. One may postulate the presence of an anticoagulant factor or mechanism in this pulmonary circuit, but what this factor may have been is not known.

In both cases presented the tumors were encountered accidentally at autopsy, but the small endothelioma in the second case had the same histologic picture as a large tumor which gave rise to severe symptoms and finally led to lobectomy (case 3 of Edwards and Taylor). Thus one cannot definitely know whether the small tumor in this 53 year old woman would have remained small, or, perhaps, would also have developed into a large tumor causing clinical symptoms.

SUMMARY

A case is reported of multiple intravascular hemangioendothelioma of the lung connected with widespread structural abnormalities of the pulmonary arteries. There was also a capillary angioma of the involved lung, and a large defect of the interventricular septum.

Another case of pulmonary endothelioma is briefly described.

The different forms of tumors arising in pulmonary vessels are described from the literature. Their interrelations and genesis are discussed.

PATHOLOGIC NATURE OF MYCOSIS FUNGOIDES

LAWRENCE BERMAN, M.D., MINNEAPOLIS

Mycosis fungoides has undergone increasing scrutiny by modern pathologists and hematologists since the original description by Alibert in 1814.[1] As the disease is neither mycotic nor necessarily fungoid in its important aspects, its name is inadequate, having been based only on the external features in the skin.

The pathologic nature of the disease is the subject of wide differences of opinion. Jaffé [2] described the disease as a tumor-like systemic disease of the skin which often extends to the lymph nodes and in rare cases also affects the internal organs. The opinion that it is essentially a neoplastic process was expressed by Warthin,[3] Montgomery and Watkins [4] and Fraser.[5] A number of French authors have favored the view that mycosis fungoides is a disorder of the reticuloendothelium.[6] In 1938 Forkner [7] reviewed the various theories as to the pathologic nature of mycosis fungoides.

Sutton and Sutton [8] defined mycosis fungoides as a chronic disorder of the skin which develops gradually and is characterized at first by lesions of an erythematous, eczematoid, urticarial or mixed type and later by irregular thickening and infiltration of the skin, with subsequent formation of nodular growths, which frequently ulcerate and form mushroom-like masses. The cutaneous manifestations preceding the development of the tumors are known to dermatologists as the premycotic lesions. In most cases there are four stages: (1) dermatitis; (2) infiltration; (3) tumor formation; (4) ulceration. Each phase has a variable morphologic picture, lasting months or years; certain phases, however, may never appear. The disease progresses to a fatal issue.

REPORT OF A CASE

The case to be described is significant because the postmortem examination made it possible to observe the relationship of the lesions of the

From the Department of Pathology, University of Minnesota.

1. Alibert, J. L., cited by Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 9, St. Louis, C. V. Mosby Company, 1935, p. 870.

2. Jaffé, R. H.: The Reticulo-Endothelial System, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, pp. 1105-1107.

3. Warthin, A. S.: Ann. Surg. **93**:153, 1931.

4. Montgomery, H., and Watkins, C. H.: Arch. Int. Med. **60**:51, 1937.

5. Fraser, J. F.: Arch. Dermat. & Syph. **12**:814, 1925.

6. (*a*) Grynfeltt, E.; Margarot, J., and Rimbaud, P.: Bull. Soc. franç. de dermat. et syph. **44**:1389, 1937. (*b*) Cottini, J. B.: Ann. de dermat. et syph. **8**: 15, 1937. (*c*) Flarer, cited by Cottini. (*d*) Berger and Vallée, cited by Cottini. (*e*) Zoon, M. J. J.: Bull. Soc. franç. de dermat. et syph. **44**:1282, 1937.

7. Forkner, C. E.: Leukemia and Allied Disorders, New York, The Macmillan Company, 1938, pp. 72-73.

8. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, ed. 9, St. Louis, C. V. Mosby Company, 1935, pp. 870-881.

skin to a disturbance of the hemopoietic function of the reticuloendothelial system.

Jan. 11, 1939, a woman 57 years old presented herself at the University Hospitals complaining of skin trouble, which had been present about five years. The past health had been good. In 1934 there appeared under the left breast a dermatitis, characterized by redness, scaling and itching. The condition gradually spread until it covered the anterior part of the thorax, both upper extremities, then the lower extremities and finally the face. In January 1938 variously located nodular lesions began to appear.

The patient was seen in February 1938 at the Mayo Clinic, where a diagnosis of mycosis fungoides was made and confirmed by a biopsy of the skin. The hemoglobin at that time was 14 Gm. per hundred cubic centimeters of blood; the red cells, 4,510,000 per cubic millimeter; the leukocytes, 4,100, with neutrophils 78 per cent, lymphocytes 9 per cent, monocytes 5 per cent and eosinophils 8 per cent. There were no immature cells. The patient received a course of radiation therapy to the skin and superficial nodes, and the lesions disappeared.

Four months later, in June 1938, nodules began again to appear in the skin. Some of the nodules coalesced and finally ulcerated and drained. They were most numerous on the sides of the neck, the left breast, the arms and the left hip. In the interval there had been a loss of 25 pounds (11 Kg.) in weight. There was no history of infection or fever.

In January 1939, approximately five years after the onset of the premycotic stage, the temperature, pulse and respirations were normal. The woman was undernourished; there was generalized pigmentation of the skin, which was probably due to the irradiation; there were nodules and a scaling eruption of the scalp. On the lateral aspects of the neck were groups of ulcerated. weeping nodular lesions, each about 1 cm. in diameter. There were many shallow ulcers on the back. A painful fissured mass in the left antecubital fossa occupied an area 5 by 3 cm. In addition, there were ulcerated nodules surmounted by encrustations on the skin of the right shoulder and right thigh. The axillary lymph nodes were slightly enlarged. On deep respirations the edge of the liver could be felt a few centimeters below the costal margin. The spleen was palpable a few centimeters below the left costal margin.

January 12 the hemoglobin content was 57 per cent; erythrocytes, 3,400,000; leukocytes, 5,900, with neutrophils 41 per cent, lymphocytes 44 per cent, monocytes 2 per cent and eosinophils 13 per cent.

February 16 there were numerous fungating masses from 1 to 6 mm. in diameter on the face, neck, chest and both arms. The lesions were raised, ulcerated and friable. Biopsies showed a histologic picture which was considered typical of mycosis fungoides. A review of the slides showed some interesting differences from the section obtained in February 1938. These will be discussed later.

The patient again received a course of radiotherapy and, as before, there was great improvement in the condition of the skin. She was discharged February 19 but was readmitted March 27 because of a reappearance of the lesions of the skin. At this time there were a large fungating ulcer on the left breast and a similar ulcer on the left arm. The patient was very weak. March 27 there were generalized brownish pigmentation, dryness and scaling of the skin and almost complete loss of hair. These changes were considered to be due to irradiation. There were a denuded area on the left breast about 5 cm. in diameter and a fungating mass

about 5 cm. in diameter on the lateral aspect of the left arm; there were similar ulcerated lesions of the left forearm and the right popliteal space. The liver's edge was 3 cm. below the right costal margin, and the spleen was palpated 5 cm. below the left costal margin. Between March 27 and April 12 the patient became much weaker. She died April 12, about five and a half years after the onset of the dermatitis. The diagnosis was mycosis fungoides. The biopsies of the skin appeared to verify the diagnosis. Blood smears were obtained the day before the patient died; they are described with the report of the autopsy.

Autopsy.—The body was markedly emaciated. The skin had a uniformly distributed brown color; it was smooth, shiny and generally dry. In a few places dry scales were present. There was no hair in the axillary or pubic regions, and there was almost complete loss of hair of the scalp and eyebrows, with some loss of eyelashes (roentgen ray). There was a widely distributed macular eruption, the macules varying in diameter from 1 mm. to 1 cm. and having a reddish purple color. They were most numerous on the upper part of the thorax and were sparse in the lower halves of the lower extremities. Encrusted ulcerations were found over the back, the right side of the thorax and the scalp; these were about 2 cm. in diameter. A deep ulcer of the skin occupied the right upper quadrant of the left breast and measured 11 by 7 cm.; the base of this ulcer was dry, and its edges were sharply defined. In the skin over the insertion of the left deltoid muscle there was a circular lesion, 3 by 2.5 cm., characterized by a ring shape, thick raised edges and a relatively smooth central portion. A similar lesion, 9.5 by 5 cm., with an ulcerated center was situated on the upper half of the left forearm. In the left antecubital fossa an ulcer 4 by 3 cm., with raised and indurated edges, had a base which was covered with a thin layer of serum. The axillary, cervical and inguinal lymph nodes were enlarged and discrete. In each axilla there were approximately thirty-five palpable nodes, which varied from 5 mm. to 4.5 cm. in diameter. In addition there was also a large number of smaller nodes. The largest nodes were soft, but on section all presented a uniform pale fleshy appearance, resembling sarcoma.

The edge of the liver was flush with the costal margin on the right; the edge of the spleen was 7.5 cm. below the left costal margin in the midclavicular line. There was a slight accumulation of fluid in the peritoneal cavity, the pleural cavities and the pericardial sac. There were no significant lesions of the heart. In each lung there were consolidations of bronchopneumonia.

The kidneys were grossly normal. The liver weighed 2,150 Gm.; the spleen, 1,355 Gm. The liver had a generally pale color, and the peripheral parts of the lobules appeared lighter in color than the central portions. There were several infarcts in the spleen. The remainder of the pulp was firm and red, and the corpuscles were not visible.

The inguinal nodes formed masses about 3 by 4 by 6 cm. on each side. About thirty-five prominent aortic nodes were found, a few of which were fused. The sections had a reddish purple color, but a few of the nodes were pale and fleshy, resembling those found in the axillary and inguinal regions.

External examination of the brain gave negative results.

Blood Smears.—At the time the smear was obtained, the hemoglobin content was 27 per cent, the red cells 1,410,000 and the leukocytes 10,200. The neutrophils were very toxic. They made up about 18 per cent of the total number of leukocytes. About 72 per cent of the leukocytes were lymphoid, and one third of these were abnormal or leukemic cells. There were reticular cells which were differ-

entiating toward the lymphocytic type. In addition, 6 per cent of the cells were very immature; they were reticular cells which were rounded and did not appear to be exerting a phagocytic function. About 3 per cent of the leukocytes were monocytes; there were occasional leukocytoid lymphocytes and rarely eosinophils. One of the features of the immature cells was that most of them were either very immature, like undifferentiated blood-forming reticular cells, or else they had very distinct lymphocytic features. Occasional intermediate forms were present (*A* in figure).

Histologic Observations.—In the brain (examined by Dr. A. B. Baker) there was fairly extensive proliferative endarteritis. Many of the small blood vessels were filled with bacteria. Scattered throughout the tissues were tiny focal lesions, some of them composed of glial nodules while others were made up of polymorphonuclear leukocytes. The bacteria might have been agonal in origin.

The thyroid, pituitary gland, breasts and ovaries were normal.

The lung showed bronchopneumonia with occasional small abscesses. In the areas surrounding the pneumonic consolidations many of the small branches of the pulmonary artery contained purulent thrombi. There was a notable increase in the number of free cells in the peribronchiolar regions, especially around bronchioles less than 3 mm. in diameter. Frequently the infiltrate occupied the entire thickness of the wall. It consisted chiefly of mononuclear cells, the majority of which resembled large lymphocytes. Plasma cells and macrophages containing brown pigment granules were also present. The perivascular reticulum was prominent.

The adrenal glands showed in the sinusoids numerous small foci of leukocytes, composed of from 10 to 100 cells, which were mostly small dark lymphocytes. One could also see plasma cells, occasional eosinophils, metamyelocytes, mature neutrophils, and macrophages containing red blood cells. There were occasional large cells with abundant cytoplasm and round nuclei containing a delicate chromatin network. They appeared to be immature cells, but they could not be identified more accurately in sections.

The liver showed moderate fatty metamorphosis, especially at the centers of the lobules. The general appearance was that of lymphatic leukemia, because of the accumulations of lymphoid cells in the portal spaces. These infiltrations consisted of lymphocytes, plasma cells and small numbers of large lymphoid cells similar to some of the cells seen in sections of axillary lymph nodes and skin tumors. There was also a rather striking activity of the reticulum. The von Kupffer cells were prominent, being increased in both number and size. They could easily be seen rounding up and becoming free in the sinusoids, but the free cells, as well as the attached hypertrophied cells, were phagocytic.

In the kidneys there were leukemic infiltrations consisting of large lymphoid cells such as one would expect to find in lymphatic leukemia.

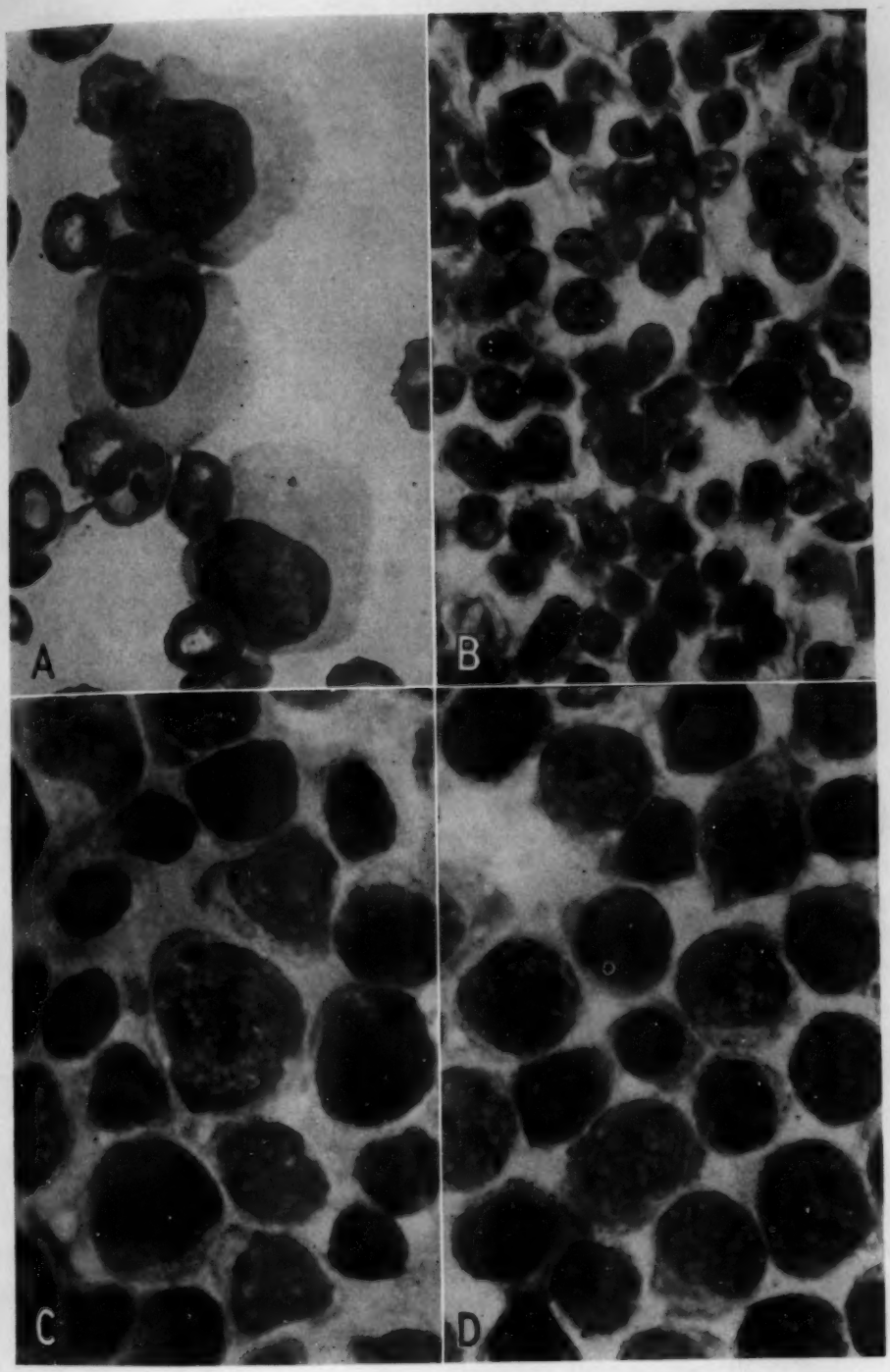
In the axillary lymph node the structure was obliterated, and the capsule was invaded. The structure was similar to that which one finds in lymphatic leukemia except that there was less uniformity in the cell type and mitotic figures were fairly abundant. Detailed examination of the cells, however, revealed that although many were definitely lymphocytes there were also very numerous large atypical lymphoid cells whose nuclear chromatin network was much more delicate than one expects in lymphocytes. The precise nature of the cells was indicated in the imprints from the node, and since the imprints from axillary nodes and those from the skin were practically identical, they may be described together.

EXPLANATION OF FIGURE

A, blood smear (May-Grünwald-Giemsa); × 1,500. Nearest the top margin is an immature cell showing distinct reticuloendothelial characteristics. The nuclear pattern resembles that of a myeloblast except that the network is coarser. The cytoplasm is irregular in outline, and occasional vacuoles are present. This is the type of stem cell found in the blood. The nuclear chromatin of the other 2 leukocytes is aggregated into coarser clumps. They represent intermediate forms between the cell near the top and lymphocytes.

B, section of a skin tumor obtained at autopsy (hematoxylin-eosin); × 900. A portion of the infiltrate is shown. Note that the nucleus of the predominant cell type is more vesicular than that of a lymphocyte.

C, imprint of a skin tumor (May-Grünwald-Giemsa); × 1,500. The predominant cell type is shown in the center of the field. It is a reticuloendothelial cell in which the nuclear material is clumped slightly, giving it a lymphocytic appearance. Note the resemblance of this cell to the immature cell shown in *A*. The cells near the upper left corner which have very dark nuclei are mature lymphocytes. *D*, bone marrow imprint (May-Grünwald-Giemsa); × 1,500. Note the replacement of the marrow by cells of lymphocytic type. The cell near the center is a normoblast.


A
B
C
D

The spleen disclosed several infarcts. The architecture was obscured. The pulp and sinusoids contained cells of lymphoid character, mainly mature lymphocytes, some plasma cells, neutrophils and occasional large lymphoid cells such as were found in the nodes and skin. In a few places, particularly under the capsule, the littoral cells appeared to be rounding up to become free in the sinuses, but here also, as in the liver, the free cells, which resembled the attached cells, were macrophages.

In regard to the bone marrow, one may say that the sections from the ribs were not satisfactory for precise description but that the marrow appeared very cellular.

Biopsy of Skin.—The section examined in February 1938, at the Mayo Clinic, showed a dense cellular infiltrate under the epidermis, without any intervening layer of normal derma. The deep boundary of the infiltrate was rather sharply defined. There were also accumulations of cells about the deep vessels, nerves and glands. From the dermatologic point of view the section was typical for mycosis fungoides, because there was a great variety of cell types, some with deeply stained nuclei and others with pale nuclei, in addition to lymphocytes and plasma cells, eosinophils, mitotic figures, pyknotic nuclei and mononuclear cells of great size with abundant, poorly circumscribed pale cytoplasm and large nuclei with one or two nucleoli and fine chromatin network, all of these features occurring in the absence of Dorothy Reed cells, the last point differentiating the infiltrate from that of Hodgkin's disease.

The skin examined in January 1939, at the University Hospitals, presented the same features but showed marked reticular hyperplasia and a tendency toward a much more uniform type of cellular infiltrate. The appearance did not differ from Hodgkin's disease of the skin except that Dorothy Reed cells were absent.

The skin tumor obtained at autopsy disclosed that there had been a considerable change. The infiltrate was much less variegated. Although there were plasma cells, eosinophils, polymorphonuclear neutrophils, tissue mast cells and lymphocytes, the chief cell was a large, distinctly outlined cell with a large round nucleus containing one or two prominent dark nucleoli and a nuclear chromatin network which was much finer than that of the lymphocyte nucleus (*B* in figure). It was only by means of the imprints that one was definitely able to identify the cells.

Imprint Material.—Imprints from the skin and peripheral nodes showed, scattered among the readily identified lymphocytes, large numbers of immature cells of reticular origin with differentiation toward the lymphocyte. They resembled closely the more differentiated of the immature cells found in the blood (*C* in figure).

Imprints from the spleen revealed that the majority of the mononuclear cells were mature lymphocytes but that immature lymphocytic cells, resembling reticular cells, were also present.

Imprints from the bone marrow showed granulocytes in various stages of development, but lymphocytes were very abundant. There were also occasional immature lymphocytes of reticular origin similar to those found in the skin, but they were not numerous (*D* in figure).

Summary of Pathologic Observations.—The diffuse macular eruption was similar to that seen in some forms of leukemia. There were tumor-like lesions in the skin, in which ulceration was a prominent feature. There was a marked increase in the number and size of palpable lymph nodes in the axillary regions, as well as enlargement of the other peripheral nodes, hepatomegaly and splenomegaly. In the lymph nodes, spleen,

liver, peribronchial regions, kidneys and bone marrow there were leukemic infiltrations consisting of cells of reticuloendothelial origin with varying degrees of differentiation toward the lymphocyte type. The cells were similar to the type cells in the skin tumors and circulating blood. The pathologic diagnosis was leukemic reticuloendotheliosis with the clinical picture of mycosis fungoides.

COMMENT

Systemic Nature of Mycosis Fungoides.—Following the review of mycosis fungoides by Paultauf [9] in 1907, the belief that involvement of the internal organs in this disease was rare became widely accepted. At present textbooks and papers emphasize this view, although it cannot be defended on the basis of evidence in the literature. Liechti [10] collected 22 authentic cases from 1895 to 1927, all showing involvement of the internal organs. He added 2 such cases of his own and concluded that Paultauf's dictum was erroneous. Sequeira [11] studied 74 cases, concluding that involvement of the internal organs was common. I have collected the reports on 60 cases of mycosis fungoides from the literature of the years 1928 to 1938, inclusive, with results as follow:

Cases reported without autopsies	42
Cases reported with complete autopsies	18
	60

Analysis of the 18 cases of mycosis fungoides reported with autopsies [12] gives the following:

Cases in which internal organs were involved	16
Cases in which involvement of internal organs was undetermined	1
Cases in which no internal involvement was mentioned	1
	18

The organs most frequently involved were the spleen, liver and lungs. The intestine was involved in 5 cases; the adrenals, in 4 cases. It is notable that in only 30 per cent of the reported cases were postmortem

9. Paultauf, cited by Liechti.[10]

10. Liechti, E.: Arch. f. Dermat. u. Syph. **154**:246, 1928.

11. Sequeira, cited by Liechti.[10]

12. Askanazy, M.: Schweiz. med. Wchnschr. **68**:806, 1938. Basu, P. N.; Menon, T. B., and Pandalai, K. G.: Brit. J. Dermat. **41**:50, 1929. Berger, L., and Vallée, A.: Presse méd. **38**:177, 1930. Chevallier, P.; Moutier, F., and Moune, R.: Bull. Soc. franç. de dermat. et syph. **42**:1417, 1935. Cornil, L.; Vigne, P., and Mosinger, M.: ibid. **44**:1394, 1937. Eschweiler, H.: Ztschr. f. Hals-, Nasen- u. Ohrenh. **41**:222, 1937. Höltkemeier, H.: Arch. f. Dermat. u. Syph. **169**:13, 1933. Howles, J. K., and Connell, J.: South. M. J. **30**:792, 1937. Keim, H. L.: Arch. Dermat. & Syph. **19**:533, 1929. Kolff, W. J.: Nederl. tijdschr. v. geneesk. **80**: 3738, 1936. Moncorps, C., and Borger, G.: Virchows Arch. f. path. Anat. **286**: 157, 1932. Portnoy, B.: Lancet **2**:1015, 1937. Samek, J., and Feuereisen, W.: Arch. f. Dermat. u. Syph. **164**:375, 1931. Zinck, K. H.: Virchows Arch. f. path. Anat. **296**:319, 1935.

examinations made and that in 16 of the 18 cases in which such examinations were made they disclosed involvement of the internal organs.

Mycosis Fungoides Considered as Lymphoblastoma.—The limits of the lymphoblastoma group are vague. Dermatologists with occasional exceptions make use of the term to include mycosis fungoides in addition to lymphatic and myelogenous leukemia, lymphosarcoma, reticuloendotheliosis and Hodgkin's disease. In order for a disease to qualify as lymphoblastoma in the dermatologic sense, it is necessary, according to Wayson and Weidman,[13] to establish a set of dermatologic circumstances and then join them with some disorder of the blood-forming organs. A premycotic stage followed by a tumor stage and death would satisfy these requirements. Thereafter the alterations of the blood-forming tissues encountered at autopsy, whether they appear as Hodgkin's disease, lymphosarcoma or aleukemic reticuloendotheliosis, complete the requirements. I believe that in this lies the source of much confusion regarding the proper classification of a given case, because it is possible to find recorded in the literature many cases of mycosis fungoides in which fundamental differences between mycosis fungoides and the other forms of lymphoblastoma cannot be stated. In spite of this, typical mycosis fungoides has been histologically defined and, recently, a mycosis fungoides cell described by Tzanck, Dreyfuss and Levy.[14]

Nonspecificity of the Clinical and Histologic Manifestations of Mycosis Fungoides.—There are now available many reports concerning the so-called mutations of mycosis fungoides into one or the other form of cutaneous or systemic lymphoblastoma. Fraser,[5] Pautrier [15] and others have reported cases of mycosis fungoides in which there were lymphatic leukemia and visceral involvement with the histologic picture of lymphosarcoma. Wile and Stiles [16] reported a mutation to Hodgkin's disease. Fraser [5] reported a case of mycosis fungoides terminating as typical Hodgkin's disease. Montgomery and Watkins [4] reported 2 cases of monocytic leukemia, one of the Naegeli type, the other of the Schilling type, in which at one time in the course the clinical picture was that of mycosis fungoides. In their review of the literature concerned with the cutaneous manifestations of monocytic leukemia they discovered that specific involvement of the skin in monocytic leukemia frequently begins by simulating the picture of mycosis fungoides.

There is no more valid argument in defense of the specificity of the histologic manifestations of mycosis fungoides. Zoon [6a] held that the polymorphous image is so typical for all forms of mycosis fungoides that it is impossible not to recognize the disease. He expressed the belief that in principle mycosis fungoides always has the same histologic pattern, differing only in the extent to which particular elements in the infiltrate occur. However, he also pointed out that when mycosis fungoides is in the tumor stage the diagnosis is extremely difficult to make from studying a single tumor, because the structure is hard to distinguish from that of other types of granuloma. Wile [17] described

13. Wayson, J. T., and Weidman, F. D.: Arch. Dermat. & Syph. **34**:755, 1936.
14. Tzanck, A.; Dreyfuss, A., and Levy, J.: Sang **12**:110, 1938.
15. Pautrier, M. L.: Bull. Soc. franç. de dermat. et syph. **44**:1307, 1937.
16. Wile, U. J., and Stiles, F., Jr.: J. A. M. A. **104**:532, 1935.
17. Wile, U. J.: Arch. Dermat. & Syph. **12**:814, 1925.

a case of mycosis fungoides in which the tumors were almost solid masses of eosinophil cells. Symmers [18] stated that the tumors in the skin in cases of mycosis fungoides are attended by histologic changes of three distinct types: (1) Hodgkin's disease, (2) reticular cell sarcoma and (3) lymphosarcoma. It is to be noted that the three types have a common origin from the reticuloendothelium. Symmers reported on 17 cases in which mycosis fungoides was diagnosed at the Massachusetts General Hospital, covering a period of ten years, and stated that in 23 per cent of the cases there were abnormal cells in the blood and that the abnormal cells varied widely as to type.

In spite of the emphatic statement by Highman [19] that a disease resembling mycosis fungoides with the blood findings of leukemia is not mycosis fungoides but leukemia and that one resembling mycosis fungoides but presenting changes in the lymph nodes characteristic of Hodgkin's disease is not mycosis fungoides but Hodgkin's disease, the admonition has not been generally deferred to by dermatologists. According to Highman's criteria, it appears that to establish the diagnosis of mycosis fungoides each case must be followed to autopsy and repeated studies of the blood must be made in order to rule out the possibility of a leukemic or other lymphoblastomatous picture in the blood or organs at any stage of the illness. As this has not been done consistently in the past one hundred and twenty-five years, there is doubt that the majority of cases could withstand close scrutiny. One would indeed be obliged to accept Symmer's view regarding the nonexistence of mycosis fungoides as an entity.

Recent Advances in the Study of Mycosis Fungoides.—A classification based on arbitrary clinical criteria can do little to clarify one's understanding of the underlying pathologic process. In the final analysis, a rational system of classification of mycosis fungoides must rest on the discovery of the etiologic factors, a task which at present seems to be insurmountable. The alternative is the precise determination of the histologic and cytologic aspects of the malignant process. For the latter purpose the technics and information offered by hematologists should be applied.

This is being done. There are increasing numbers of cases of mycosis fungoides reported, particularly in the French literature, in which complete studies are available, either clinical or postmortem, including examinations of blood smears and comparison of the observations with those from biopsies of the marrow and imprints of involved lymph nodes and skin. Cottini [6b] described the hematologic aspects of mycosis fungoides as observed in 3 cases. He obtained specimens of the skin, blood smears, sternal marrow, imprints of lymph nodes and skin tumors. Using the May-Grünwald-Giemsa staining technic, he was able to demonstrate reticulohistiocytic cells (Ferrata's terminology) in the blood and in imprints of lymph nodes and skin tumors. He therefore considered mycosis fungoides a disease of the reticuloendothelial system. Cottini's photographs of his imprinted material are more convincing than the evidence which has hitherto been indicated in sections.

18. Symmers, D.: Arch. Dermat. & Syph. **25**:1, 1932.

19. Highman, W. J.: Arch. Dermat. & Syph. **13**:522, 1926.

SUMMARY

According to modern writers, mycosis fungoides is a dermatologic disease having neoplastic characters and probably arising from the reticuloendothelium.

An examination of case reports indicates that the prevailing opinion that involvement of the internal organs is rare has been based on incomplete evidence. Involvement of internal organs is the rule rather than the exception.

The clinical criteria for the diagnosis of mycosis fungoides may be satisfied by different pathologic entities within the lymphoblastoma group.

The case described is evidence that mycosis fungoides is a systemic disease affecting the hemopoietic function of the reticuloendothelial system, since it satisfies the requirements of typical mycosis fungoides and leukemic reticuloendotheliosis.

Support is offered to Cottini's view that the unknown factor which is the cause of the different aspects of mycosis fungoides acts electively on the reticuloendothelial system and is capable of provoking the diffuse and generalized picture of the systemic form as well as the circumscribed localized manifestations familiar to dermatologists.

GIANT CELL CARCINOMA OF THE THYROID

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It is generally accepted that carcinomas occasionally lose the morphologic characteristics by which they may be identified as epithelial in origin. Various authors have emphasized the polymorphism of malignant epithelial cells, particularly with reference to the so-called carcinosarcomas, and have pointed out the factors effective in the simulation of connective tissue cells. When the resemblance to sarcoma includes the presence of collagenous fibers, the interpretation becomes more difficult. The production of collagen is so closely associated with the fibroblast that intimate association of cells and fibers in a tumor is commonly accepted as evidence of a connective tissue origin of the tumor. On the other hand, it has been shown that fibers may appear in a tumor independent of its cell type. This fact has hardly received the emphasis which it deserves. I shall report a case of primary tumor of the thyroid which exhibits the structure of both carcinoma and sarcoma. This tumor, interpreted as a giant cell carcinoma, illustrates the manner in which a sarcoma may be simulated both as to morphologic appearance and as to the presence of collagenous fibers.

REPORT OF A CASE

A white woman 30 years of age had had a goiter for many years. During the summer of 1937 there was a rapid increase in size of the mass in the neck. Pressure symptoms, particularly dysphagia, resulted. On September 11 thyroidectomy was undertaken. Much difficulty was encountered in the procedure. The right lobe, which was but partially fixed, was removed intact. The left lobe was found to be fixed to surrounding structures, hemorrhagic and necrotic throughout, and so far as possible its substance was removed by scraping. The postoperative course was stormy. The patient was continually febrile, and there was a persistent troublesome cough. Hoarseness developed, and laryngoscopic examination revealed a cadaveric left vocal cord. Roentgenograms of the chest showed numerous circumscribed densities within the lung fields. There was a rapid increase in size of the incompletely removed mass in the neck. After a steady downhill course, characterized by increasing dyspnea, cyanosis, restlessness and fever, death occurred on October 5.

Autopsy.—The body was that of a well developed, moderately obese white woman 172 cm. in length and weighing about 180 pounds (81.5 Kg.). Rigor was present, and there was dependent hypostasis. There was no cyanosis, no edema and no jaundice. The pupils were regular; each measured 6 mm. in diameter. The neck was crossed in its anterior inferior aspect by an incompletely healed incised wound. There was sanguineous drainage from the left extremity of the wound. A large, ill defined mass, fixed to both skin and underlying tissues, was present on the left side of the neck.

From the Department of Pathology, University of Minnesota.

The peritoneal cavity presented no abnormality. The appendix was normal. The diaphragm reached the level of the fourth rib on the right and the fourth interspace on the left. The pleural cavities were dry; there were a few fibrous adhesions over the lower posterior aspect of the right lung. Attached to the left parietal pleura at the level of the seventh rib posteriorly were two white, irregularly rounded firm nodules, each measuring about 2.5 by 3 cm. The pericardial sac was normal. The heart weighed 325 Gm. and presented no abnormality.

The right lung weighed 1,175 Gm.; the left, 950 Gm. Each was diffusely studded with smoothly circumscribed nodules measuring from a few millimeters to 4 cm. in diameter. There were a few such nodules on the pleural surfaces. Most nodules could be shelled with ease from the surrounding pulmonary tissue. On section they presented a varying appearance. Many were firm, opaque and white. Others were diffusely hemorrhagic and necrotic. Some presented irregularly bordered homogeneous colloid-like masses. In some areas tumor tissue could be demonstrated in the smaller bronchi. A few nodules were of distinctly different character. The cut surfaces of these were smooth and slightly translucent and had much the appearance of the cut surface of a colloid goiter.

The spleen weighed 175 Gm. The capsule was smooth, the cut surface deep red and the pulp soft. The liver weighed 2,100 Gm.; the cut surface was cloudy. The gallbladder and bile ducts were without change. The gastrointestinal tract was normal throughout. The pancreas and adrenals were normal. The right kidney weighed 150 Gm.; the left, 175 Gm. Other than a moderate cloudy swelling no change was noted. The pelves, ureters and bladder were normal. The uterus, tubes and ovaries were normal. There was a minimal degree of atherosclerosis of the abdominal aorta. No abnormality of abdominal or peripheral lymph nodes was noted. Small nodes at the hilus of each lung were grossly free from tumor tissue. Examination of the head and exploration of the neck were not permitted.

The operative specimen consisted of two distinct portions. One was an encapsulated mass, the right lobe of the thyroid; the other was composed of a group of fragments from the left lobe of the thyroid. The single mass measured 8 by 7 by 6 cm. and weighed 200 Gm. Throughout its greater extent the surface was smooth; numerous projecting nodules caused it to be somewhat lobulated. On section adenomatous areas were seen, demarcated by dense fibrous bands, which showed focal areas of calcification. Somewhat more than half the mass was represented by firm opaque white tissue, within which were areas of necrosis. This tissue encroached irregularly on the adenomatous areas and extended through the capsule on one surface, where there were attached fragments of skeletal muscle. The tissue removed from the left lobe totaled, according to the operative report, a volume about half that of the other mass. These fragments were friable and hemorrhagic. Section revealed islands of opaque white tissue.

Microscopic Observations.—The microscopic observations relative to the operative specimen and the pulmonary lesions only will be considered. The bronchial nodes were free from metastases. All the tissue was fixed in solution of formaldehyde U. S. P. Sections were stained with hematoxylin and eosin, azocarmine, Bielschowsky's silver impregnation, phosphotungstic acid–hematoxylin and Masson's trichrome stains.

For the most part the structure of this tumor is that of a sarcoma. As may be seen in figure 1, it is composed of irregularly polyhedral cells, among which are scattered numerous multinucleated giant cells. The cells vary widely in size;

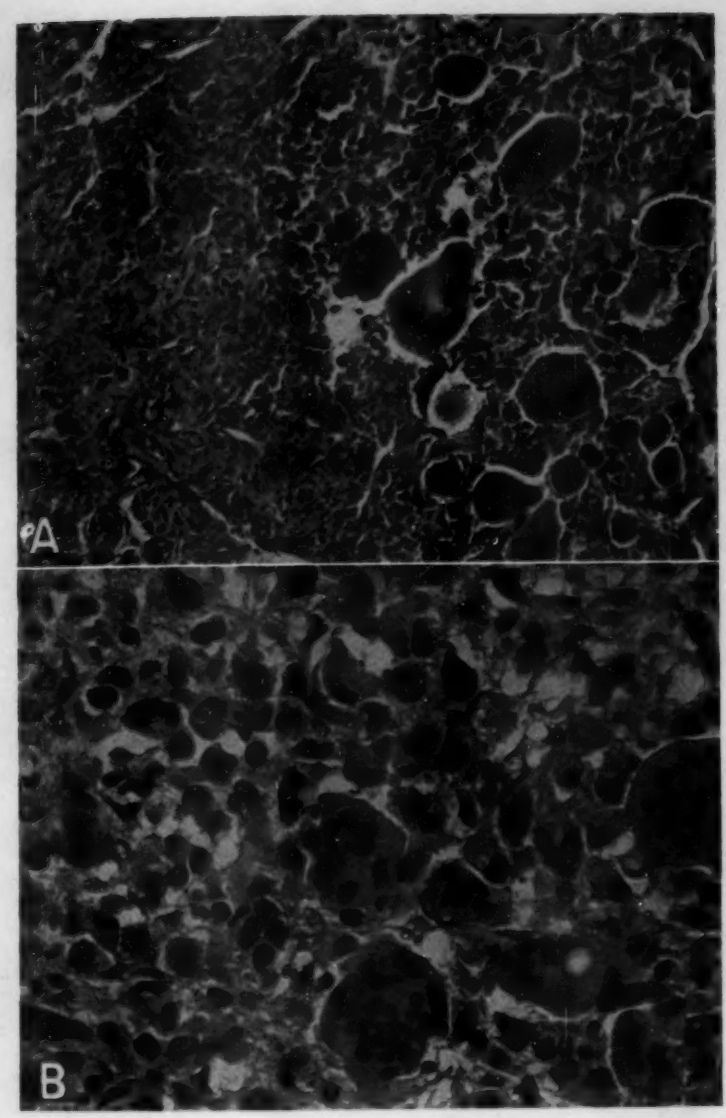

Fig. 1.—*A*, section showing the usual sarcoma-like appearance. Note the giant cells among irregularly polymorphous cells. Hematoxylin-eosin; × 150. *B*, higher magnification of an area of the section shown in *A*. Hematoxylin-eosin; × 350.

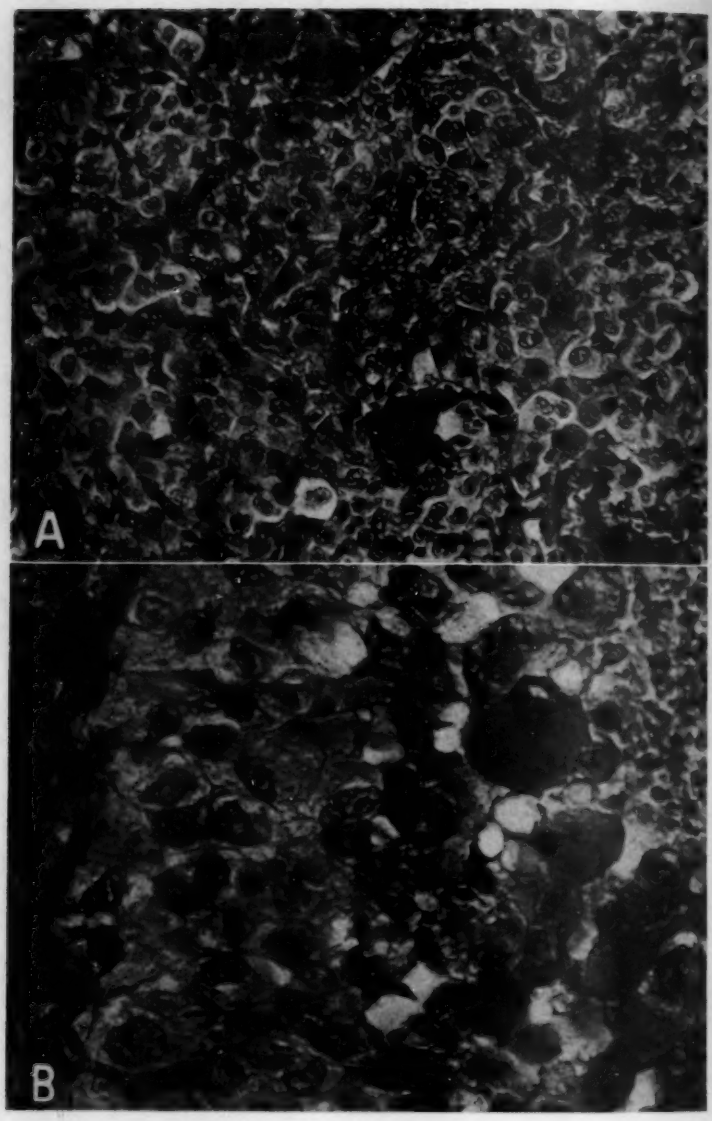

Fig. 2.—*A*, section of the tumor in the left lobe of the thyroid, showing the epithelial arrangement of the cells. Hematoxylin-eosin; × 250. *B*, higher magnification of the area shown in *A*. Note cell boundaries. Hematoxylin-eosin; × 650.

their boundaries are indistinct and frequently drawn out into long processes. The nuclei are commonly round to oval and hyperchromatic. An occasional cell is of larger size and contains a lobulated giant nucleus. Mitotic figures are frequently encountered. The giant cells present a homogeneous cytoplasm and sharply rounded or irregularly branched cell boundaries, and contain from a few to approximately a hundred small, usually centrally located oval nuclei. Necrosis and hemorrhage are prominent. In many random sections healthy tissue is found with difficulty. The stroma is generally inconspicuous, although well formed capillaries are present in most sections. In sections from the operative specimen the sarcomatous structure predominates. Tumor tissue is seen to invade adenomas, the dense connective tissue of the capsule and adjacent skeletal muscle. In some areas, however, the structure is modified. Where growth is apparently limited by the dense framework of the gland the cells present a more orderly arangement. They are closely packed, and there is a tendency toward formation of epithelial cords. Here cell boundaries may occasionally be identified. In sections from both right and left lobes of the thyroid islands of cells, such as those illustrated in figure 2, are seen. In these areas the structure is obviously epithelial. Through careful study of such areas transitions from epithelial cells to the surrounding polymorphous and giant cells are demonstrable. Conclusive transitions may not be shown in any one microscopic field and consequently cannot be illustrated as such.

Two types of pulmonary metastases were noted grossly. The sections show that by far the majority of these are sarcomatous; the structure is essentially that already described and illustrated (fig. 1). The variations should be mentioned. The grossly noted colloid-like masses within nodules are composed of a homogeneous acidophilic material. Adjacent tumor cells present no characteristic arrangement. At the periphery of many of the nodules the cells are more regularly arranged. Often small groups of cells, particularly those isolated in pulmonary alveoli, present distinct cell borders. The giant cells in the metastases are more variable as to size and number. They are more numerous in the larger, older lesions than in the smaller. Individual cells with giant nuclei are common, and there are all gradations between these and the multinucleated forms.

The minority of the metastases show the structure of adult thyroid tissue. Here are seen colloid-filled vesicles of irregular size (fig. 3 *A*). Not all contain colloid; the epithelial structure is, however, the same. In figure 3 *B* an epithelial metastasis is seen adjacent to, but distinct from, a sarcomatous metastasis. This independence predominates. On the other hand, as shown in figure 4 *A*, the two types of tissue are found together in the same metastatic nodule. The vesicles formed here contain no colloid. They form an integral part of the general structure and merge completely with the sarcomatous portion. This illustration emphasizes the intimate relationship of these seemingly independent tissues in a manner similar to that of the transitions demonstrated between epithelial and sarcomatous portions of the primary tumor.

Sections stained with azocarmine (Mallory-Heidenhain) show in most instances a profusion of blue fibers. These are most prominent in relation to the vessels of the stroma and to the pulmonary parenchyma where it has not been destroyed. However, in some sections nearly every cell is paralleled by a fiber. The fibers are most frequently fine but in many areas are moderately coarse. They are never found in association with the giant cells and are frequently absent from the larger, more regularly arranged cells at the periphery of the metastatic nodules. Fine fibers pass from among intraalveolar groups of cells to the alveolar walls. Sections impregnated with silver similarly show large numbers of fibers of the same

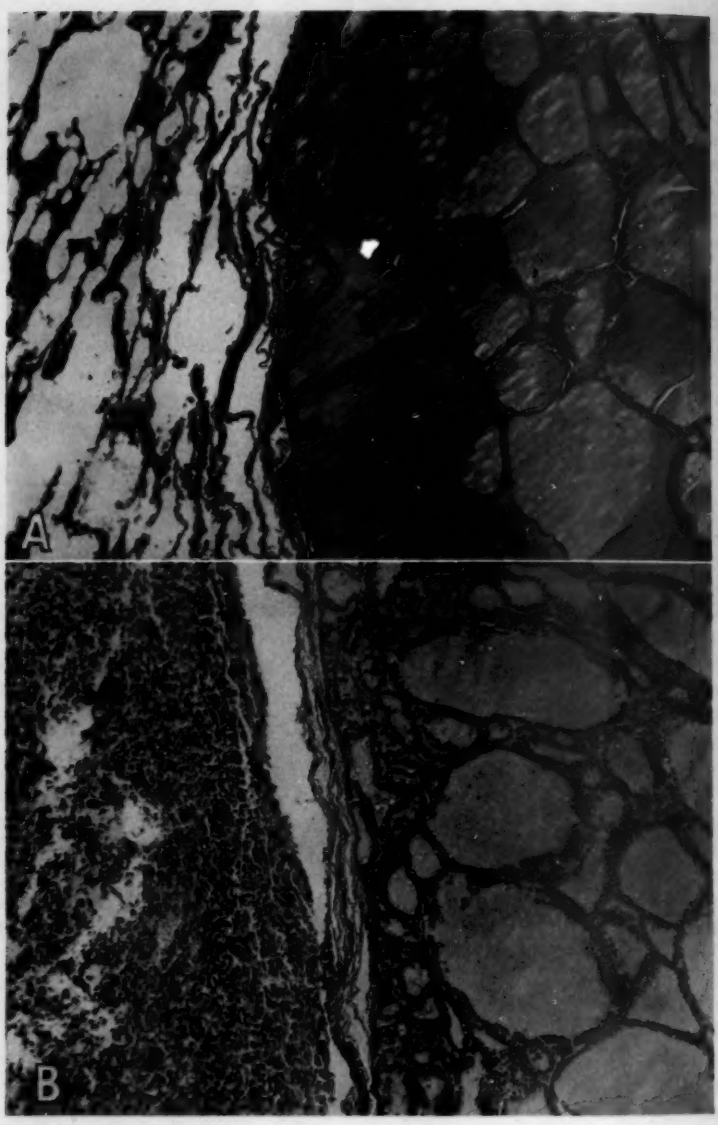

Fig. 3.—*A*, pulmonary mestastasis showing the structure of adult thyroid tissue. Hematoxylin-eosin; × 65. *B*, pulmonary metastases. A portion of a nodule having the structure of adult thyroid tissue is adjacent to but distinct from a sarcoma-like nodule. Hematoxylin-eosin; × 65.

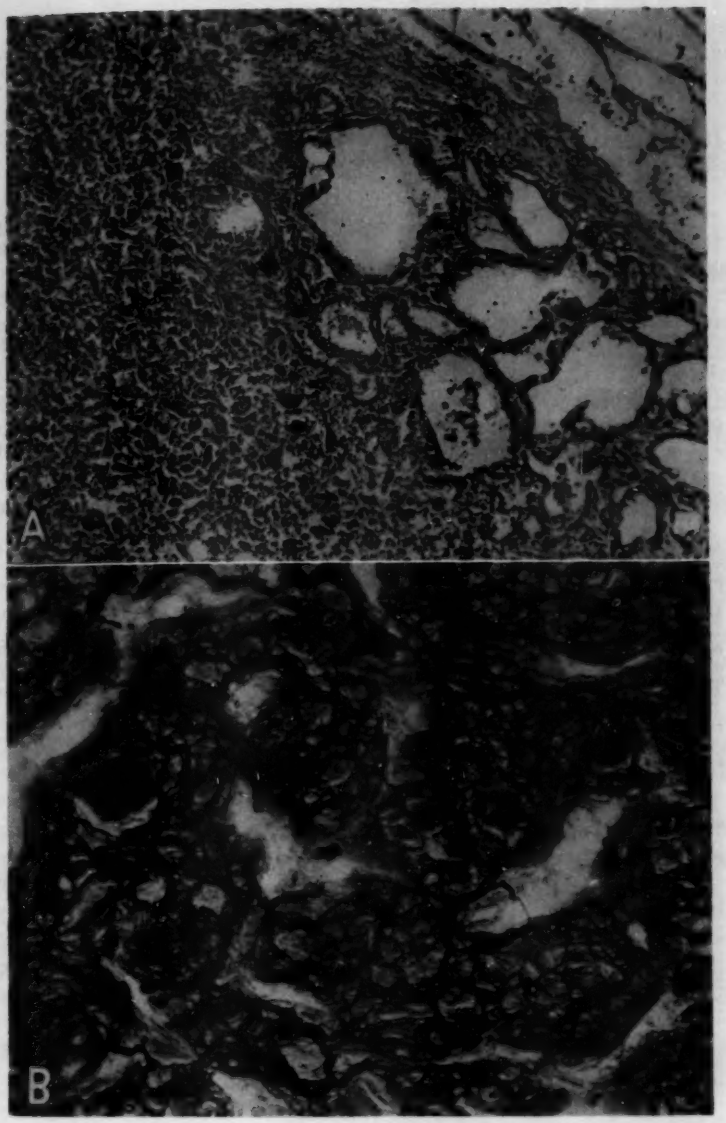

Fig. 4.—*A*, section of a pulmonary metastasis showing partial differentiation into thyroid-like vesicles. Hematoxylin-eosin; × 65. *B*, section from an area similar to that shown in figure 1 *A*. Note the intimate relationship of cells and fibers. Bielschowsky's stain; × 350.

character and distribution. As seen with azocarmine they are most prominent in relation to the stroma but regularly pass among the cells and surround small cell groups (fig. 4*B*).

In sections stained with phosphotungstic-acid hematoxylin and Masson's trichrome stain there was no evidence of the presence of fibroglia fibers in relation to tumor cells.

COMMENT

It is believed that this tumor may be justifiably interpreted to be wholly of epithelial origin. Acceptable transitions from frankly epithelial to sarcoma-like portions are demonstrable. It may be further said that the presence of collagenous fibers among the cells in various portions of the tumor offers no objection to this interpretation. The term "collagen" may be used synonymously with and for reticulum. Although there has long been disagreement as to the relationship between argyrophil and common collagenous fibers, the best evidence indicates that they are identical.[1] Irrespective of the debatable origin of the fibers,[2] studies of the reticulum of tumors indicates a lack of relationship between the cellular constituents and the amount of and distribution of reticulum present. Foot and Day [2b] found reticular fibers to be most abundant in rapidly growing tumors and pointed out that they were as numerous in relation to epithelial cells as they were in relation to connective tissue cells. Although usually confined to the periphery of cell masses in carcinomas, the fibers frequently penetrate among the cells. Tureen and Seelig [3] concluded from a similar study that the distribution of reticulum depends not on the differentiation of the tumor but on the character of the stroma in which it is growing. Cohn [4] found that special stains when applied to undifferentiated tumors failed to give an unequivocal diagnosis.

The lack of dependence on the cell type of a tumor for the appearance of collagenous fibers is well illustrated in figures 5 and 6. These tumors are unquestionable carcinomas of the penis and cervix, respectively. Each presents in part a frankly epithelial architecture while in other areas, such as those illustrated, the structure has been modified. Here the cells are separated and are frequently irregularly spindle shaped. As seen with azocarmine and silver stains, fibers appear among the cells more or less in direct relation to the lack of epithelial structure.

In the carcinoma of the penis fibers may be seen ramifying diffusely among the cells and paralleling the drawn-out cytoplasmic processes. While most numerous in relation to the demonstrable fibroblastic stroma, there are so many fibers at a distance from this stroma that they appear to be dependent only on the degree to which epithelial structure in the tumor itself is lost. A similar but less pronounced relation exists in

1. (*a*) Mallory, F. B., and Parker, F.: Am. J. Path. **3**:515, 1927. (*b*) Maximow, A. A.: Arch. Path. **4**:557 (Oct.) 1927.

2. (*a*) Foot, N. C.: Am. J. Path. **1**:341, 1925. (*b*) Foot, N. C., and Day, H. A.: ibid. **1**:431, 1925. (*c*) Wolbach, S. B.: ibid. **9**:689, 1933. (*d*) Mallory and Parker.[1a]

3. Tureen, L. L., and Seelig, M. G.: Arch. Path. **15**:498 (April) 1933.

4. Cohn, M.: Virchows Arch. f. path. Anat. **259**:30, 1926.

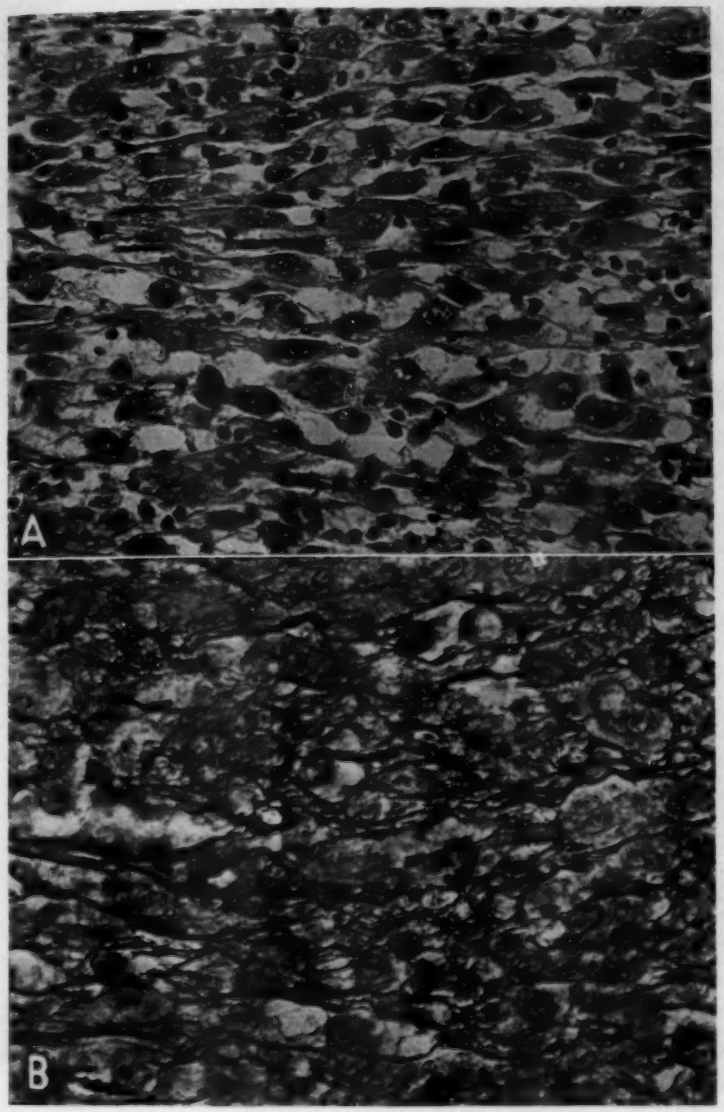

Fig. 5.—*A*, squamous cell carcinoma of the penis. Note spindling and separation of cells. Hematoxylin-eosin; × 350. *B*, same section as *A*, showing intimate relation of cells and fibers. Bielschowsky's stain; × 350.

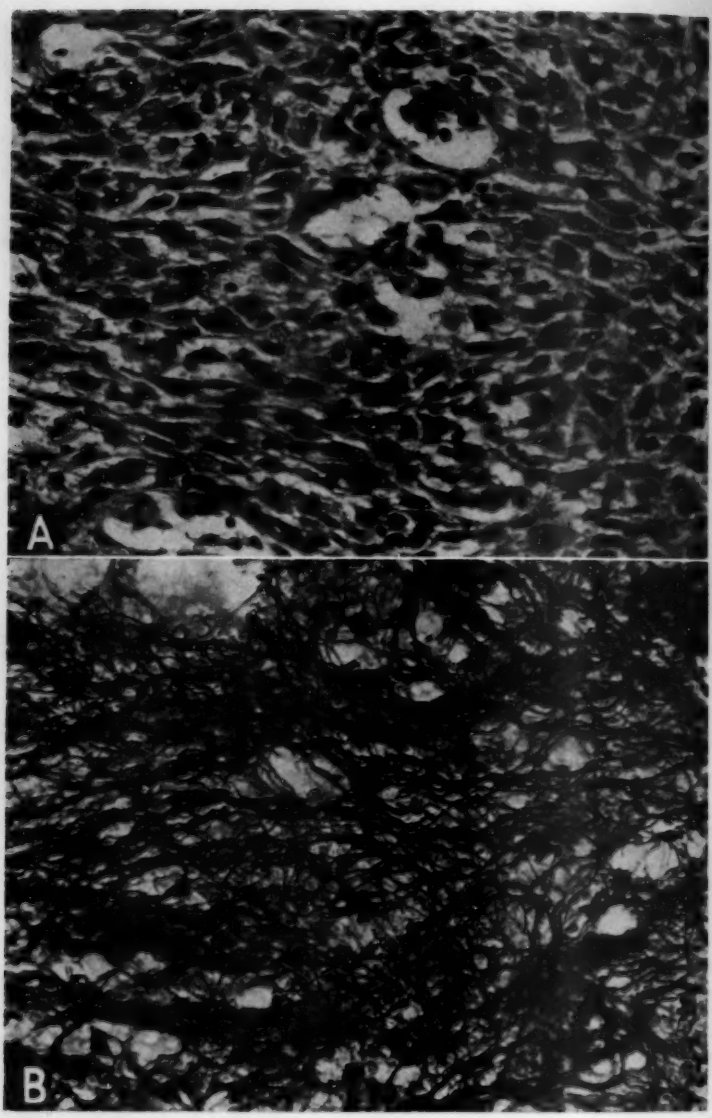

Fig. 6.—*A*, squamous cell carcinoma of the cervix. Note spindling and separation of cells. Hematoxylin-eosin; × 350. *B*, section from an area similar to that shown in *A*. Fine fibers continuous with those of the stroma ramify among the tumor cells. Bielschowsky's stain; × 350.

the carcinoma of the cervix. Here ramifications of the fibers bear a more direct relation to the stroma. They are most numerous at the periphery of sheets and masses of tumor cells, but wherever the cells are separated from one another fibers ramify irregularly among them.

Thus the relationship of cells and collagenous fibers in the tumor of the thyroid is paralleled in carcinomas of the penis and cervix. There is no reason for postulating, merely on the basis of lack of differentiation and an absence of epithelial structure in the tumor, that the cells have assumed fibroblastic properties in the ordinary sense. Rather it must be appreciated that fibers may appear among the cells of a tumor independent of its derivation and be related to those cells only as regards the extent to which they maintain an epithelial relation to one another.

The manifestations of this thyroid tumor have an important bearing on the question of the so-called carcinosarcoma.[5] The thyroid is one of the most frequently described sites of carcinosarcoma. Saphir and Vass,[6] in 1938 collected the majority of the reported cases. These authors, as well as Ewing,[7] Kettle [8] and others have emphasized the extremely doubtful authenticity of such tumors, not only of the thyroid but of other organs as well. The belief that the altered morphologic character of malignant epithelial cells has led to errors of interpretation is substantiated in the tumor described here. The extreme polymorphism which may be exhibited by an epithelial tumor is aptly illustrated, and the ease with which it can be mistaken for a sarcoma may be readily appreciated. The abundance of collagenous fibers exaggerates the sarcomatous appearance. That the presence of such fibers cannot be accepted as proof of connective tissue origin has been pointed out. Although the name "carcinosarcoma" is descriptive of the appearance of such a tumor, its use in the sense that both epithelial and connective tissue derivatives are participating in the neoplastic process cannot be justified.

This tumor may be rightly classified with the giant cell carcinomas of the thyroid as described by Clute and Smith,[9] Clute and Warren,[10] Smith, Pool and Olcott [11] and Haagensen.[12] Smith [13] and Ewing,[7] in particular, emphasized the pleomorphism of carcinomas of the thyroid. Ewing's statement that " . . . the mesoblastic origin of most of the sarcomas reported in the literature is highly improbable, and that the occurrence of true sarcoma in man still requires demonstration" is supported by the observations in tumors of this kind.

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5. Herxheimer, G.: Beitr. z. path. Anat. u. z. allg. Path. **44**:150, 1908. Saltykow, S.: Verhandl. d. deutsch. path. Gesellsch. **17**:351, 1914.

6. Saphir, O., and Vass, A.: Am. J. Cancer **33**:331, 1938.

7. Ewing, J.: Neoplastic Diseases, ed. 3, Philadelphia, W. B. Saunders Company, 1928, pp. 961 and 1018.

8. Kettle, E. H.: Proc. Roy. Soc. Med. (pt. 3) **12**:1, 1919.

9. Clute, H. M., and Smith, L. W.: Arch. Surg. **18**:1, 1929.

10. Clute, H. M., and Warren, S.: Am. J. Cancer **15**:2563, 1931.

11. Smith, L. W.; Pool, E. H., and Olcott, C. T.: Am. J. Cancer **20**:1, 1934.

12. Haagensen, C. D.: Am. J. Cancer **15**:2063, 1931.

13. Smith, L. W.: Arch. Path. **10**:524 (Oct.) 1930.

SUMMARY

A primary malignant tumor of the thyroid gland which exhibits the appearance of both carcinoma and sarcoma is reported. Transitions between the apparently dissimilar tissues are considered evidence for a common epithelial origin, and the tumor is interpreted as a giant cell carcinoma. It is further shown that the presence of collagenous fibers in the sarcomatous portions of the tumor is not inconsistent with this interpretation.

Dr. E. G. Benjamin supplied the clinical data and the operative specimen, and Mr. H. W. Morris contributed the photographic work.

PURPURA HAEMORRHAGICA ASSOCIATED WITH WIDESPREAD DEPOSITS OF CRYSTALLINE MATERIAL: RETICULOENDOTHELIOSIS

HARRY AGRESS, M.D.,* AND MARGARET G. SMITH, M.D., ST. LOUIS

Widespread pathologic changes involving the reticuloendothelial system have been described frequently in association with a great variety of clinical and pathologic syndromes under numerous titles, among them "reticuloendotheliosis." It has been possible to place most of the conditions described in several fairly distinct general groups. Occasionally one occurs which defies classification because of some unique feature. It is one of this nature that the authors have encountered and have deemed of sufficient interest to report in detail.

REPORT OF A CASE

A 55 year old married white woman entered Barnes Hospital May 24, 1937. In November 1936 she noted that her urine was red and that there were numerous bruises over her body which had appeared spontaneously. The ecchymoses became more pronounced within a few weeks and were accompanied by severe epistaxis, rectal bleeding and hemorrhage from the gums. The family history was irrelevant, and the patient's past history was without interest except that she had always bruised easily.

On admission she was well nourished and well developed. The temperature was 36.8 C. (98.2 F.). The skin was pale and slightly icteric. Numerous ecchymoses were present over the entire body. The gums were swollen, tender and discolored, and bled readily. The chest and heart were normal. The blood pressure was 122 systolic and 74 diastolic. The edge of the liver was 2 finger-breadths below the costal margin. The spleen extended to the level of the umbilicus. There was no appreciable lymphadenopathy.

The red blood cell count was 2,720,000; the leukocyte count, 4,500; the hemoglobin, 54 per cent (Sahli); the Schilling differential hemogram, not notable. The platelets were estimated to number 148,000. The bleeding time was ten and one-half minutes (Duke method); the clotting time, twenty to thirty-five minutes (normal by the modified Howell technic employed). Clot retraction was poor. The Kahn test of the blood was negative. The urine showed a trace of albumin and occasional leukocytes but no red blood cells or casts.

It was believed that this was an instance of idiopathic thrombopenic purpura haemorrhagica, despite the fact that the number of platelets was not markedly reduced. A series of relatively small doses of roentgen rays of high voltage was given in an attempt to stimulate platelet formation, but during this treatment marked diminution in all the blood elements occurred. Roentgen therapy was discontinued, and the patient was then treated with fairly large doses of pent-

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nucleotide and vitamins and with blood transfusions. The blood counts rose following the transfusions but soon receded to subnormal levels. The red cell count varied between 2,140,000 and 3,500,000, the leukocyte count between 1,500 and 4,500, and the hemoglobin percentage between 40 and 50 (Sahli). The number of platelets dropped as low as 50,000 and then rose to 220,000. Hemolysis began in 0.40 per cent sodium chloride and was complete in 0.28 per cent sodium chloride. Cultures of blood, made because the patient's course was febrile, were negative. The urine showed albumin in small amounts at all times. No examination was made to determine whether this was of the Bence Jones type. The only determination of blood protein was made during the terminal days of the illness, and the serum protein was reported as 7.1 per cent. The protein fractions were not studied. The nonprotein nitrogen was 29 mg. per hundred cubic centimeters of blood during the early days of her illness and rose to 182 mg. when she was near death.

About one month after her admission to the hospital a sternal puncture was performed. In smears of the marrow were a number of large histiocytic cells which contained needle-like or rod-shaped cytoplasmic inclusions (fig. 1 *A*). The number of inclusions in individual cells varied; in some cells there were but few; in others the cytoplasm was completely replaced. These structures stained deep azure with a combination of May-Grünwald and Giemsa stains. The normal elements of the marrow showed no morphologic alterations. A careful search of the peripheral blood then revealed monocytic cells which contained small rods suggestive of bacilli or of the Auer bodies found in certain leukemic cells.

Splenectomy was performed. The spleen measured 20 by 10 by 7.5 cm. After operation the white blood cell count rose to as high as 15,400, the platelet count to 250,000, the erythrocyte count to 3,670,000 and the hemoglobin percentage to 61. The clinical course, however, was rapidly downhill, terminating in uremia two weeks after operation.

Autopsy, Shortly After Death.—The body, that of a well nourished middle-aged white woman, showed extensive ecchymoses. In the left upper abdominal quadrant there was a recent operative wound with ecchymoses about its edges.

The peritoneal cavity contained 50 cc. of clear yellow fluid. The operative bed was hemorrhagic. On the epicardium a number of petechial hemorrhages were present.

The lungs were congested and the lower lobes partially atelectatic. Throughout both lungs were localized areas of hemorrhage.

The stomach contained 500 cc. of black fluid and the intestinal tract black fecal material, but no bleeding points were found.

The liver was small and had a finely granular surface with a tawny color. When sectioned, it contained more fibrous tissue than was normal, and the lobular markings were indistinct.

The pancreas was firm and large, weighing 180 Gm.

The adrenals were large, weighing 24 Gm.

The right kidney weighed 210 Gm. and the left 160 Gm. They had finely granular surfaces, scattered over which were small, grayish white flecks and petechial hemorrhages. On the cut surface the architecture was disturbed by small, grayish white areas, similar to those visible on the capsular surface. Petechial hemorrhages were seen in the renal pelves.

The mesenteric, retroperitoneal and mediastinal lymph nodes were slightly enlarged and firm. Some of the nodes presented minute hemorrhages on their surfaces and when sectioned.

The marrow of the ribs, sternum, vertebrae and femur was grayish red and cellular. No tumor formation was noted.

Microscopic Examination.—The spleen, removed at operation, was so altered that on superficial examination it suggested a glandular organ with alveolar arrangement (fig. 2 *C*). This glandular appearance was the result of marked hyperplasia of the littoral reticulum of dilated sinuses. The cytoplasm of these cells contained closely packed globular or crystalline bodies (fig. 2 *D*) which stained well with a number of stains. With hematoxylin and eosin they stained pink, with the

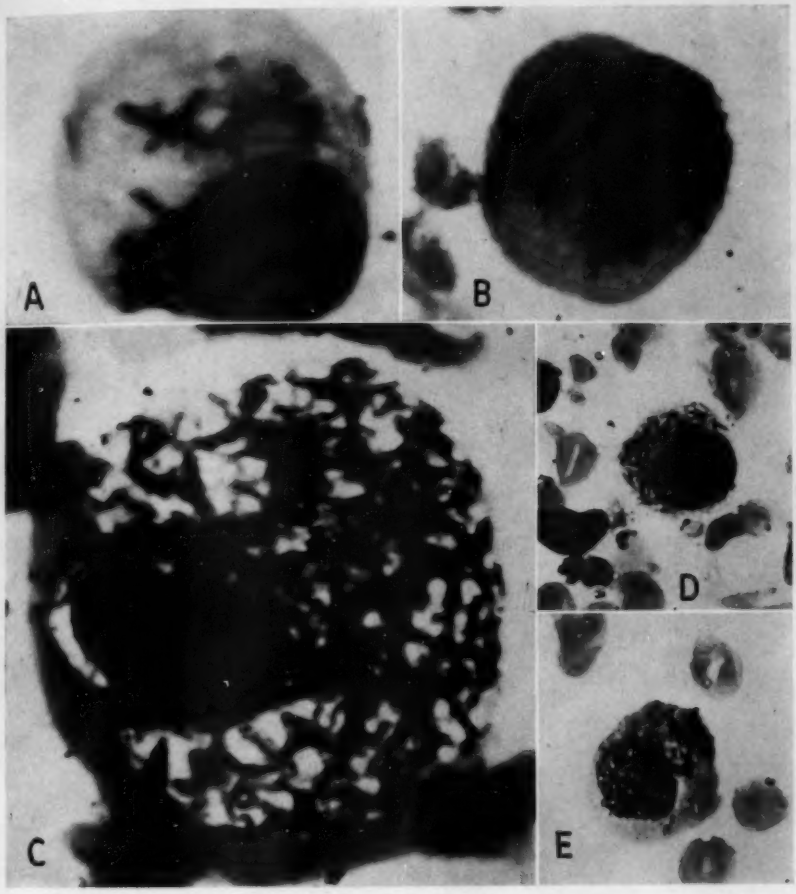

Fig. 1.—Cells displaying the characteristic crystalline inclusions. *A* (× 1,520), *B* (× 1,520) and *D* (× 1,000) are from sternal marrow obtained by puncture. *C* (× 1,520) and *E* (× 1,000) are from imprint preparations of the lung.

Dominici stain deep blue, with the Unna-Pappenheim stain bright deep red, with Masson's polychrome stain bright red and with Foote's modification of the Bielschowsky stain pinkish brown. In addition to the littoral reticulum cells, there were some free cells of the reticuloendothelial type, both in the splenic sinuses and in other parts of the spleen, containing similar cytoplasmic inclusions. The

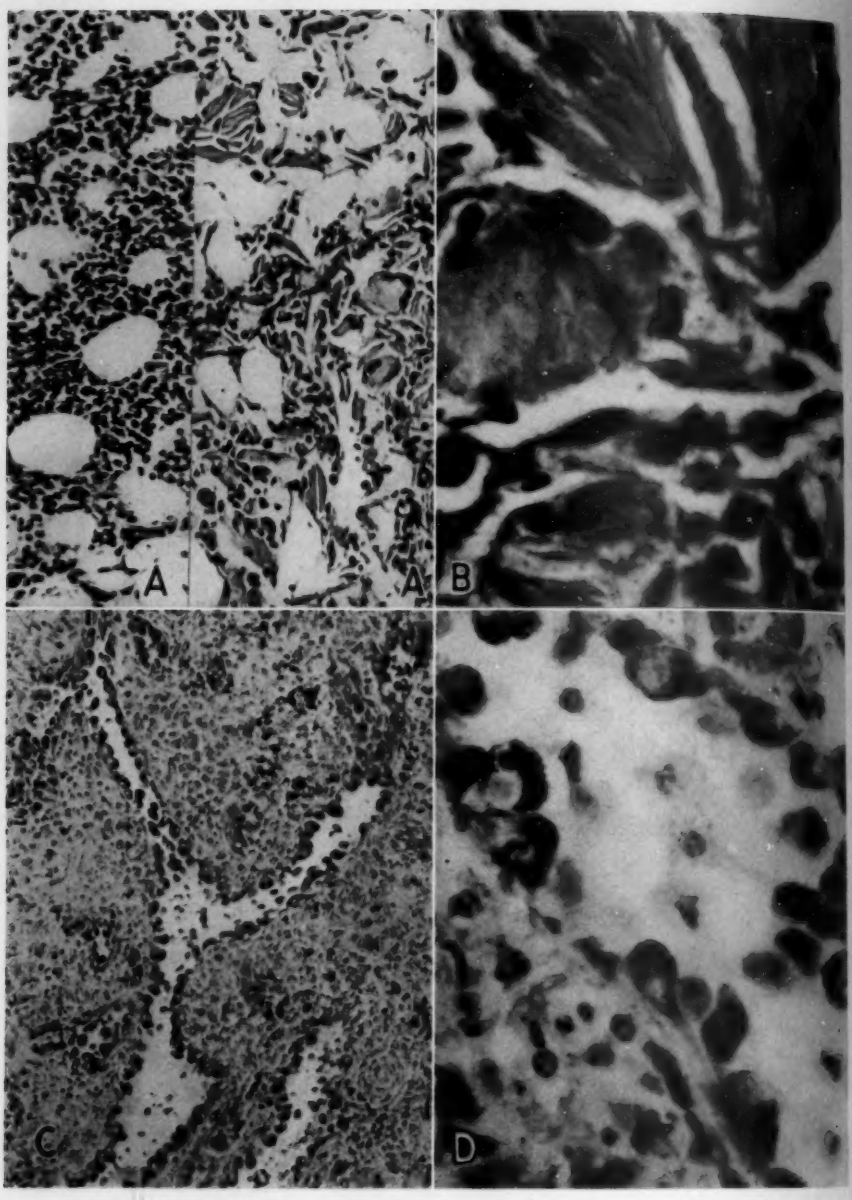

Fig. 2.—*A* (× 120) is a composite of bone marrow obtained from different sites. On the left is fatty marrow, with relatively normal cellular elements, and on the right are crystalline deposits replacing the marrow cells. *B* (× 615) is an enlargement of *A* showing the bundle-like arrangement of crystalline material. *C* (× 120) is a section of spleen showing dilated sinuses and a scalloped appearance of sinus linings. *D* (× 615) is a higher magnification of *C* showing globular cytoplasmic inclusions in cells lining sinuses.

malpighian corpuscles were diminished in size and in number. The capsule was moderately thickened, but throughout the rest of the spleen there was only a slight increase in collagen fibers.

The marrow from the femur, ribs and sternum showed a variable picture (fig. 2 *A*). Some areas were mildly hyperplastic and others hypoplastic, the general tendency being toward hypoplasia with replacement of marrow by fat. All normal

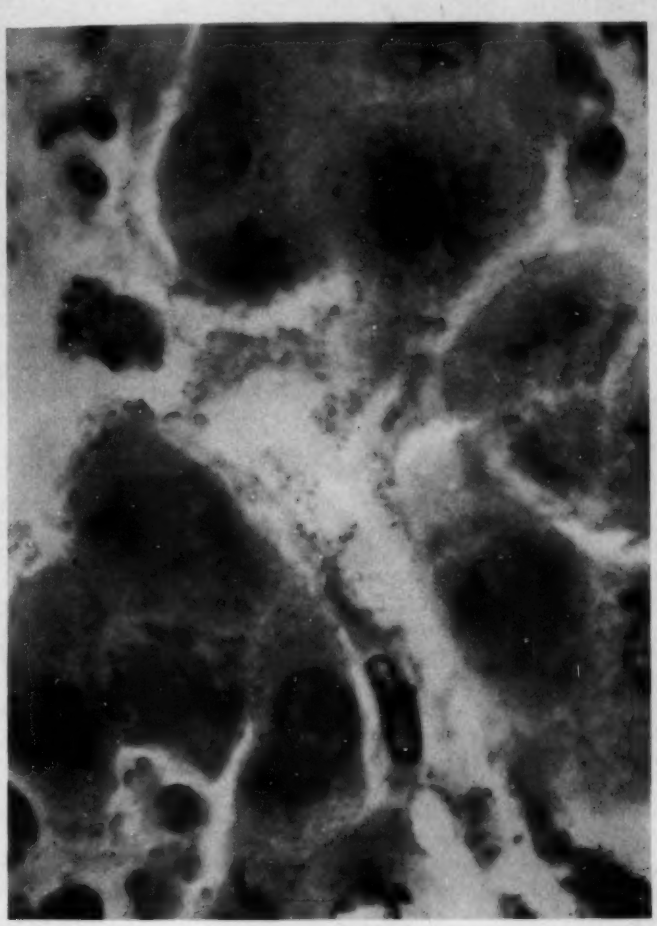

Fig. 3.—Liver cells showing crystalline and globular inclusions (× 1,240).

marrow elements were present. The megakaryocytes appeared most obviously reduced in number. The major qualitative variation from normal was the presence of large collections of crystalline-like material, which could be seen readily under low power (fig. 2 *A*) and which took all stains. These crystals were grouped in small polygonal bundles (fig. 2 *B*). Some of the bundles were definitely within huge cells, a limiting membrane and occasionally an eccentric nucleus of the reticuloendothelial type being visible. The individual crystals were needle-like and varied from 15 to 40 millimicrons in length. They were insoluble in ether,

nitric acid, chloroform, glacial acetic acid, dilute hydrochloric acid, alcohol and hot water. They were not doubly refractile in polarized light. Smaller cells with globules and crystals in the cytoplasm similar to those observed in the spleen were also seen, but there was no apparent transition from these smaller cells to the larger ones just described. The small cells corresponded to those seen in the sternal marrow.

The renal tubular epithelium was swollen, and in some areas all or many of the cells contained rods and granules similar to those seen in the splenic reticulum. In some places the epithelium was shed as a cast, and there was evidence of regeneration in the form of low cuboidal epithelium. In other places the basement membrane, as well as the lining cells, was destroyed. Polymorphonuclear leukocytes were present in a few tubules, especially about the masses of crystalline material. Red blood cells were commonly observed in addition to hyaline acidophilic casts. An occasional free cell of the type seen in the spleen and bone marrow was present in the interstitial tissue. The walls of some of the smaller arterioles showed a moderate degree of thickening and hyalinization. Some hyalinized glomeruli were present. In addition, many glomeruli showed slight thickening of the capillary membranes and at times some hyperplasia of the epithelium of the tuft. Crystals or globules were not observed in the glomerular epithelium.

The adrenals presented a striking picture. Almost every cell in the cortex was engorged with crystals and globules. Crystals and globules were present also in conspicuous, irregularly shaped large phagocytic cells lying about the capillaries and in the supporting tissue of the entire gland. The medullary cells contained few, if any, of these foreign elements.

The liver showed extensive periportal fibrosis with regeneration of bile ducts. In and around these portal areas there were numerous cells containing crystalline and globular inclusions (fig. 3). These also occurred in parts of the liver which were otherwise normal. The participation of the Kupffer cells in this process was no greater than that of the liver cells. The epithelium of the bile ducts was normal.

In the lungs there were large localized areas of hemorrhage and edema and other areas of partial atelectasis. Especially in the latter there was noted an increase in free round cells, both lymphocytes and larger mononuclear cells. The latter cells contained globular or crystalline cytoplasmic inclusions. Some histiocytes were present which contained ingested carbon particles, iron pigment and red blood cells, as well as these inclusions. Rarely a giant cell of the Langhans type was present. The bronchial epithelium appeared normal.

The heart muscle was normal. In the perivascular fat about a large blood vessel there were mononuclear cells containing the curious globules or crystals.

Imprint preparations from the spleen, lungs and bone marrow were stained with a combination of May-Grünwald and Giemsa stains. In all the imprints there were found cells varying from 15 to 25 millimicrons in diameter, similar to those seen in the sternal marrow obtained by puncture (fig. 1).

In a section of one small mesenteric lymph node, free cells similar to those seen in the spleen were present, but the reticulum was not as obviously involved as in that organ.

COMMENT

We have been able to find but one report of a case in which histologic changes apparently identical with ours are portrayed. The author [1] of this report considered the condition he described as mul-

1. Glaus, A.: Virchows Arch. f. path. Anat. **223**:301, 1916-1917.

tiple myeloma. However, the plate illustrating the bone marrow is identical with our figures *2A* and *B*. Myelomatous tumor nodules containing crystals were described in the ribs, vertebrae, sternum and long bones. The crystals were found in abundance in cells in the lymph nodes and testes. Abrikosoff and Wulff [2] described a case of multiple myeloma of the "myeloblastic type" in which needle-like, rodlike and rectangular crystals were found in the periphery of an "actinomycotic-like" tumor nodule in the rib. The description is that of classic multiple myeloma, and there was not the widespread occurrence of crystals noted in our material. These authors showed by chemical analysis that the crystals which they observed were closely related to Bence Jones protein. A more recent report by Ritchie and Meyer [3] described "crystals of unknown composition in phagocytes in widely distributed regions," but the photomicrographs accompanying the paper do not display changes that are comparable to those which we have described here. However, it is not unlikely that the crystals which they discussed are in some way related to those of which we write. These authors considered their case one of "aleukemic reticulo-endotheliosis." In addition to the crystals reported by the authors cited, various unknown crystalline inclusions, other than cholesterol crystals, have been noted in isolated cells by a number of authors.[4]

Every attempt on our part to classify the condition presented has met with some major objection. There is little to suggest any primary blood dyscrasia. The blood picture seems to be of the same order as that of the so-called panmyelophthisis reported to occur with carcinomatous metastases in bone; i. e., it is the result of a replacement of marrow elements of all types. It is obvious, however, that this condition does not represent a neoplastic process. Its only manifestation in common with multiple myeloma is the presence of peculiar crystalline material, possibly protein. In multiple myeloma, however, the crystals described have been limited to tumor nodules and to renal tubules, whereas in the condition we have described the crystals were widely disseminated. Crystalline inclusions associated with disease of the reticulo-endothelial system have been described only by Ritchie and Meyer,[3] and they observed that "the disturbance was . . . sharply limited to the reticulo-endothelial system . . ." The obvious widespread involvement of this system in our case would incline us to classify the condition among the reticuloses already reported were it not for the marked involvement of unrelated tissues, e. g., the adrenals, liver cells and renal tubular epithelium.

A possible physiologic basis for the changes that have occurred in this case is suggested by the many recorded observations (chiefly experi-

2. Abrikosoff, A., and Wulff, F.: Verhandl. d. deutsch. path. Gesellsch. **22**: 270, 1927.

3. Ritchie, G., and Meyer, O. O.: Arch. Path. **22**:729, 1936.

4. (*a*) Dubreuil, G., and Favre, M.: Arch. d'anat. micr. **17**:302, 1920-1921. (*b*) Maximow, A., in von Möllendorff, W.: Handbuch der mikroskopischen Anatomie des Menschen, Berlin, Julius Springer, 1927, vol. 2, p. 262. (*c*) Osgood, E. E., and Ashworth, C. M.: Atlas of Hematology, San Francisco, J. W. Stacey, Inc., 1937, p. 102, fig. 307.

mental) dealing with phagocytosis of colloid substances and vital dyes.[5] It has been observed in these experiments that the involvement of organs varies with the amount, nature and concentration of the colloids used and with the route of administration. Apparently, reticuloendothelial cells have the greatest affinity for colloid substances and phagocytose them in a more or less selective manner. However, under certain conditions many other cells assume what has been designated as "facultative phagocytosis." Downey[6] called attention to the fact that vital staining is not necessarily a property of reticuloendothelial cells alone and that this property is one of functional rather than morphologic distinction. Jaffé[7] went so far as to express the opinion that all cells of the body with the possible exception of ganglion and bone cells may become phagocytic. Suffice it to say that there is adequate evidence that under certain conditions phagocytosis not only by the various components of the reticuloendothelial system but also by unrelated tissues occurs.

With this evidence in mind, it seems logical to assume that the histologic picture in our case was the result of extensive phagocytosis. A suggestion as to the nature of the substance phagocytosed was derived from a recent observation of spontaneous in vitro crystallization of a protein in the blood serum of a patient with the clinical picture of multiple myeloma.[8] An autopsy was not performed in this instance, and therefore it could not be determined whether this crystallization occurred also in the tissues. It has been repeatedly observed[9] that spontaneous crystallization of protein, possibly of the Bence Jones type, may occur in the urine, and that the crystals may be present in the urinary tubules of patients with multiple myeloma, but the observation of such crystals in the blood serum is apparently unique. It seems possible that in the present case there occurred a rare systemic disease, probably metabolic in character, which resulted in spontaneous crystallization of a similar protein and its subsequent phagocytosis after the fashion of the phagocytosis of colloid elements.

SUMMARY

A case of purpura haemorrhagica is reported in which unique changes were observed due to the presence of crystalline material in the components of the reticuloendothelial system and in other unrelated tissues. It is conjectured that this anatomic picture was the result of a metabolic disturbance. In the discussion the possibility that the crystalline material was protein in nature has been considered.

5. Lubarsch, O.: Klin. Wchnschr. **4**:1248, 1925. Maximow,[4b] p. 451. Okamoto, H.: Virchows Arch. f. path. Anat. **250**:275, 1924. Delaney, P. A.: Anat. Rec. **43**:65, 1929. Duthie, E. S.: J. Path. & Bact. **33**:547, 1930.

6. Downey, H.: Anat. Rec. **12**:429, 1917; **15**:103, 1918.

7. Jaffé, R. H., in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 2, p. 972.

8. von Bonsdorff, B.; Groth, H., and Packalen, T.: Folia haemat. **59**:184, 1938.

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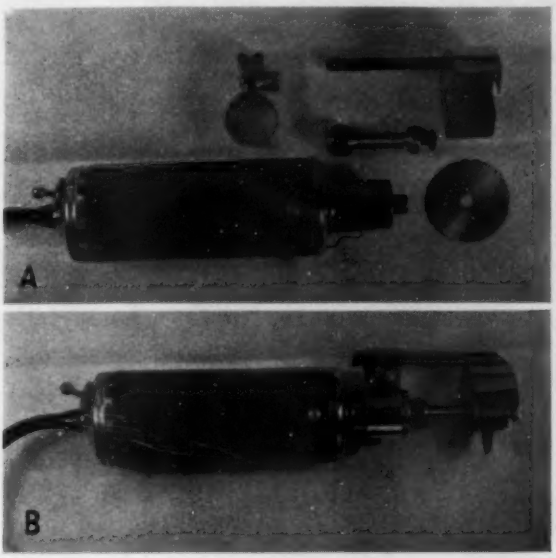
Laboratory Methods and Technical Notes

AN INEXPENSIVE ELECTRIC BONE SAW

C. Allen Payne, M.D., Grand Rapids, Mich.

The use of the electric saw in the necropsy room to remove the calvarium is rapidly increasing because it both lessens the work and decreases the time necessary for this procedure. The high cost of the usual orthopedic and other electric bone saws has led to a search



A, elements of an electric bone saw; *B*, saw assembled.

for an instrument of this type which would combine the features of economy, simplicity, ease of handling and safety. For a total cost of $15.50 my associates and I have assembled a saw which has proved satisfactory in all these respects for over a year.

DESCRIPTION OF INSTRUMENT

The source of power of the instrument illustrated is a Coe Electric Handpiece Model 3, the chuck of which has been removed and substituted by an extension chuck, 1½ by ⅜ inches (3.5 by 1 cm.), made by our engineering department. The free end of the chuck is pegged and fitted with a screw and washer in order that it may hold a saw blade similar to those used with the Albee bone saw. A sleeve

From the Department of Laboratories, Blodgett Memorial Hospital.

with a clamp for holding an adjustable metal guard is fitted over the front end of the instrument and held in place by a screw and nut. This fitting serves two purposes: First, different-sized guards are necessary for the various-sized blades, and second, the compactness of the instrument necessitates the removal of the guard before the blade can be detached.

The complete instrument weighs 1 pound 4 ounces (565 Gm.) and is convenient to handle. We have found that the greater ease of handling is helpful in making additional angles in the calvarium, not possible with the larger and heavier saws, so that when the cap is replaced it fits tightly and produces a better cosmetic result. This instrument is not quite as powerful as the Albee or other similar instruments, but we find that this is not a disadvantage in its use. This saw has also been used in the preparation of bone specimens for the museum and in cutting specimens for decalcification.

Notes and News

University News, Promotions, Resignations, Appointments, Deaths, Etc.—Rudolf Kronfeld, professor of dental pathology at the Chicago College of Dental Surgery, Loyola University, died Feb. 13, 1940, at the age of 38.

William H. Woglom has been named active head of the Institute of Cancer Research at Columbia University in the place of Francis Carter Wood, emeritus.

Sir Patrick Laidlow, deputy director of the National Institute for Medical Research, England, and head of its department of experimental pathology, has died at the age of 58 years.

The John Phillips Memorial Medal of the American College of Physicians has been awarded to René J. Dubois of the Rockefeller Institute for Medical Research for his investigations of microbic cells and his isolation from soil of a bacillus that produces a lethal substance for pneumococci and other gram-positive bacteria.

George H. Whipple has been appointed a member of the editorial board of the ARCHIVES OF PATHOLOGY, taking the place of the late Alfred Stengel.

Society News.—The next annual meeting of the American Public Health Association will be held in Detroit, Oct. 8 to 11, 1940. The secretary of the association is Dr. R. M. Atwater, 50 West Fiftieth Street, New York.

The Association of American Physicians will hold its next annual meeting in Atlantic City, N. J., May 7 and 8, 1940.

Carl V. Weller has been chosen editor of the *American Journal of Pathology*, and Tracy B. Mallory, assistant editor.

The new officers of the American Association of Pathologists and Bacteriologists are: S. Bayne-Jones, president; S. R. Haythorn, vice president; H. T. Karsner, secretary; A. R. Moritz, treasurer.

Philip E. Smith, professor of anatomy at Columbia University, has been elected president of the American Association of Anatomists.

The new officers of the American Society for Experimental Biology are: Shields Warren, Boston, president; Jesse Bollman, Rochester, Minn., vice president; Harry P. Smith, Iowa City, secretary-treasurer. By virtue of his office, Shields Warren will serve as chairman of the Federation of the American Societies for Experimental Biology, the next meeting of which will be held in Chicago in March 1941.

The eighth American Scientific Congress will be held in Washington, D. C., May 10 to 18, 1940, under the auspices of the government of the United States of America. One section will be on public health and medicine.

Special Course in the Pathology of Tumors.—A course on tumors will be offered at the University of Minnesota Medical School, June 19 to July 26, by James S. McCartney, associate professor of pathology.

Abstracts from Current Literature

To Save Space the Original Titles of Abstracted Articles Sometimes Are Shortened

Experimental Pathology and Pathologic Physiology

Injections of Gum Acacia in Bile Fistula Dogs. R. G. Metcalf and W. B. Hawkins, Am. J. Path. **15**:429, 1939.

In dogs with bile fistula repeated intravenous injections of acacia result in enlargement of the liver due to accumulation of acacia in the liver cells. The plasma proteins progressively decrease and are maintained at a level much below normal as a result of the presence of acacia within the blood stream and the liver. Acacia within the liver cells does not seriously interfere with the cells' ability to form bile salts or to eliminate bile pigments, and it does not disturb the enterohepatic cycle of bile salt metabolism when bile salts are fed; the fed bile salt is absorbed and excreted promptly into the bile. Bile and blood cholesterol metabolism are not altered, as the relation between the total blood cholesterol and the esters of cholesterol is maintained within the normal range. In the dog with bile fistula the total cholesterol of the blood decreases, but this is related to faulty absorption of fats due to total deprivation of bile. Chloroform and carbon tetrachloride when given by mouth cause injury of the liver with reduction in bile salt formation. The injury in 1 instance was severe enough to cause spontaneous bleeding with death from hemorrhage, indicating interference with the formation of fibrinogen and prothrombin.

From Authors' Summary.

Experimental Hypertension. A. Blalock, S. E. Levy and R. D. Cressman, J. Exper. Med. **69**:833, 1939.

Unilateral renal ischemia superimposed on intestinal ischemia has resulted in prolonged elevation of the arterial blood pressure in a high percentage of the animals that were studied.

From Authors' Summary.

Experimental Production of Digestive Tract Ulcerations. A. Penner and A. I. Bernheim, J. Exper. Med. **70**:453, 1939.

In order to simulate the vasomotor reactions in shock, epinephrine hydrochloride was injected intraperitoneally into dogs, cats, rabbits and guinea pigs. Lesions in the digestive tract were produced which seemed to be identical grossly with those observed by others in human beings in shock, but there were certain microscopic differences in the dog and cat due to the presence in these animals of arteriovenous anastomoses in the submucosa. The changes produced experimentally indicate that vasospasm may result in necrosis.

Spontaneous Mediastinal Emphysema. C. C. Macklin, M. Rec. **150**:5, 1939.

That atelectasis may be a real danger is emphasized, because, by diminishing the lung volume, it induces overinflation of the surrounding lung substance, which in turn predisposes to leakage of air into the interstitial tissue. The air does not diffuse indiscriminately but selects the vascular sheaths because they lie immediately under the sites of the many small ruptures in the overdistended alveolar bases and because from the point of inlet these sheaths form the line of least resistance toward the root of the lung. Pressure of air in the sheaths on the pulmonary blood vessels may give rise to lateral pain in the chest, which is often observed to precede the symptoms and signs of air in the mediastinum. Air reaches the

mediastinum via the pulmonary roots and accumulates first in the middle and posterior spaces. If it extends forward around the parietal pericardium, it gives rise to the crunching sound reported by Hamman. It may spread up into the neck and axillas, down into the retroperitoneum or laterally into the interstitial tissue of the opposite lung. Anginoid pain may be due to direct pressure on the coronary arteries. The circulatory embarrassment may lead to death, although many patients get well of themselves.

FROM AUTHOR'S ABSTRACT.

PARATHYROID HORMONE AND VITAMIN D NEPHRITIS. E. CHOWN, M. LEE and R. CURRIE, J. Path. & Bact. **49**:273, 1939.

Details are given of the treatment of rats with parathyroid hormone and with vitamin D. The former treatment frequently, and the latter rarely, led to chronic nephritis. The genesis of parathyroid nephritis is described. It is considered to be due to deposition of calcium within and outside tubules, with obstruction, leading to atrophy of some nephrons and dilatation of others.

FROM AUTHORS' SUMMARY.

AUTOPLASTIC SPLENIC GRAFTS. R. M. CALDER, J. Path. & Bact. **49**:351, 1939.

The growth of autoplastic splenic grafts in rats and mice is described, and it is concluded that the reticulum cell of the adult spleen is responsible for most of the elements found in the fully grown graft. The development of the reticulum cell into the phagocyte, the endothelial cell and the lymphocyte is described, and the opinion is expressed that this is the cell most likely to play an active part in pathologic hyperplasia of the spleen.

FROM AUTHOR'S SUMMARY.

PRODUCTION OF GALLSTONES BY VITAMIN A DEFICIENCY IN GUINEA PIGS. V. ERSPAMER, Virchows Arch. f. path. Anat. **302**:766, 1938.

Many have described the formation of urinary calculi in animals maintained on a diet deficient in vitamin A. A few have described the formation of concretions in the biliary passages under similar conditions. In guinea pigs fed a vitamin-deficient diet Erspamer observed the presence of masses in the hepatic ducts and in the gallbladder. These were not true concretions. They contained no cholesterol and no inorganic elements. They were formed from degenerated and necrotic epithelium cast into the lumens of the ducts. Ulceration of the ducts and gallbladder was noted. Vitamin A has an important role in maintaining a normal state of certain epithelia.

O. T. SCHULTZ.

Pathologic Anatomy

GIANT CELLS IN TONSILS IN CHICKENPOX. T. H. TOMLINSON JR., Am. J. Path. **15**:523, 1939.

Apparently well authenticated chickenpox developed in a 5 year old Indian girl three days after tonsillectomy. Histologic examination of the tonsils showed numerous giant cells seemingly identical with those previously reported as occurring during the prodromal stage of measles.

FROM AUTHOR'S SUMMARY.

"CARDIAC CIRRHOSIS" OF THE LIVER. H. M. KATZIN, J. V. WALLER AND H. L. BLUMGART, Arch. Int. Med. **64**:457, 1939.

An investigation of an unselected series of 2,000 consecutive cases in which autopsy was performed was undertaken in order to learn the incidence, types and degrees of hepatic fibrosis in cases of congestive heart failure and to make a comparison of these findings with those in cases in which congestive heart failure was absent.

There were 286 cases of chronic passive congestion, and there was an increase of hepatic fibrous tissue in 95, or 33 per cent. In the 1,714 cases in which chronic passive congestion was absent the incidence of hepatic fibrosis was 12 per cent. The causal significance of chronic passive congestion in the production of hepatic fibrosis was emphasized by the increasing incidence and severity of the fibrosis with increasing duration of congestive heart failure. The incidence of each of the various kinds of fibrosis except biliary fibrosis was higher in the 286 cases of congestive failure than in the remaining 1,714 cases. The only type of increase in connective tissue peculiar to the cases of cardiac decompensation was central fibrosis, for with a single exception no instance of central fibrosis was found in the 1,714 cases in which autopsy disclosed an absence of congestive failure. Of particular interest was the finding of increased periportal connective tissue in 23 per cent of the 286 cases of congestive failure, as compared with an incidence of 9 per cent in the 1,714 cases in which chronic passive congestion was not present. While central fibrosis was found only in cases of chronic passive congestion, portal fibrosis was found in a larger percentage of such cases than in cases in which chronic passive congestion was absent. This suggests that chronic passive congestion with resulting anoxemia, by increasing the susceptibility of the hepatic tissue, is also a contributing factor to fibrosis in the portal areas.

The evidence obtained in this investigation has clarified the meaning of the term "cardiac cirrhosis." Cardiac cirrhosis, signifying morphologic increase in connective tissue in the liver consequent to congestive heart failure, is present in the majority of patients who have suffered from even mild congestive heart failure for nine months or more; the fibrosis may be central or portal or both. Clinical cardiac cirrhosis, signifying extreme fibrosis which clearly results from chronic passive congestion and which leads to portal obstruction, occurs but is rare. Among the 286 cases of congestive failure there were only 15 in which marked but not necessarily predominant ascites required abdominal paracentesis. The clinical diagnosis of cardiac cirrhosis can be made only rarely, since it must be based on the finding of preponderant ascites, a small liver in spite of elevation of the venous pressure and particularly a palpable spleen. Not infrequently, however, the liver may be enlarged. In such cases, although increased fibrous tissue is present and the surface of the liver is generally nontender and sometimes somewhat irregular, the dilatation of the sinusoids leads to the increase in size of the liver. In a patient with a clinical diagnosis of cardiac cirrhosis one may find portal or central fibrosis, singly or in combination, or diffuse patchy fibrosis.

From Authors' Summary.

The Argentaffine Cells and Pernicious Anemia. W. Jacobson, J. Path. & Bact. **49**:1, 1939.

1. The argentaffine cells occur in the cardia and the pylorus but are practically absent from the corpus of the stomach in man and the pig. They are very numerous in the duodenum and quite frequent in other parts of the small intestine; they occur also in the colon and appendix, though to a lesser degree. 2. The granules of the argentaffine cells give a positive murexide reaction, reduce ammoniac silver nitrate and form a diazo dye with diazo compounds. From this it is concluded that they contain a purine compound. 3. The granules have a yellow color and in the ultraviolet ray show an orange fluorescence, which is composed of two bands with maxima at 5,550 and 6,100 angstroms. 4. In an alkaline medium the fluorescence of the granules appears yellow-green before it is destroyed; in strong acids it appears faint red after prolonged treatment. 5. The ultraviolet absorption spectrum shows a maximum at 2,700 angstroms as measured on a 10 micron section through a carcinoid tumor. 6. Observations 2 to 5 suggest that the granules of the argentaffine cells contain a pterine. 7. The granules contain also a carbohydrate which gives a positive Kiliani test and a Schiff reaction. 8. There is a striking parallelism between the distribution of the argentaffine cells of man and the pig and the localization of the principle active against pernicious anemia in the mucosa of the gastro-

intestinal tract. 9. In 12 cases of pernicious anemia in which early fixation of tissue was possible the argentaffine cells were either completely or almost completely absent. 10. In 2 cases of sprue with macrocytic anemia an almost complete absence of argentaffine cells was noted. 11. In macrocytic anemias which do not respond to liver treatment (3 cases) and in secondary anemia the argentaffine cells are not affected or are affected only to a lesser degree. 12. Observations 8 to 11 suggest that the argentaffine cells play a part in normal erythropoiesis.

From Author's Summary.

Nonsyphilitic Interstitial Pneumonia of Infants. O. Ammich, Virchows Arch. f. path. Anat. **302**:539, 1938.

Ammich reports a study of interstitial pneumonia as observed in 14 infants in whom syphilis was excluded as a factor. Histologically and clinically the nonsyphilitic form of interstitial pneumonia is not to be distinguished from syphilitic pneumonia alba. The condition was observed chiefly in premature infants who lived from 1 day to 2½ months. The pulmonary lesion is considered a reaction of immature tissues to a variety of nonspecific noxa. Ammich holds that the pneumonia seen in syphilitic infants is not necessarily the result solely of the action of the infecting agent but may be the expression also of the reaction of an immature human organism. The 3 full term infants of the series, who lived four to eleven months, were examples of hypoplastic constitution; in these infants, also, immaturity of the tissue was held to be the essential factor.

O. T. Schultz.

Pathologic Chemistry and Physics

Solubility of Hemosiderin in Acids. R. D. Lillie, Am. J. Path. **15**:225, 1939.

Hemosiderin after fixation with solution of formaldehyde U. S. P. is rather slowly soluble in dilute acids, best in oxalic, then in sulfuric and then in nitric, formic and aqueous hydrochloric acids. It is very slowly soluble in hydrochloric acid–alcohol and almost insoluble in 20 per cent acetic acid. Higher concentrations of acid increase the speed of solution, and elevation of the temperature facilitates solution of at least the iron component of hemosiderin. Fixatives that contain acids but no formaldehyde often completely remove hemosiderin or alter it so that brown pigment containing no demonstrable iron is produced. The presence of formaldehyde in the fixative often protects hemosiderin against acetic, formic and hydrochloric but not against sulfuric acid. Alcohol is inferior to solution of formaldehyde U. S. P. as a fixative for hemosiderin. Formaldehyde in the fixing fluid tends to make hemosiderin more resistant to subsequent extraction with acids. The alteration of the solubility of the iron in hemosiderin treated with certain fixatives as compared with that treated with other fixatives and with unfixed hemosiderin indicates that iron exists in a protein combination. This concurs with the views of Hueck, Schmidt, Neumann and Arnold. The persistence of brown granular pigment containing no demonstrable iron in areas of old hemorrhage after the disappearance of hemosiderin has often been noted. The present findings show that a similar pigment may be produced from hemosiderin by the action of acids in the fixing fluids or by the action of warm acids on previously fixed material. This indicates that hemofuscin may be derived from hemosiderin by the loss of the iron content of the latter. It seems clearly indicated that the iron of hemosiderin is in the ferric state. Even powerful reducing agents fail to reduce it to the ferrous form, and even after conversion into iron sulfide a part of the iron appears to remain in, or very promptly to revert to, the ferric state. Considerable variation in the speed of solution of hemosiderin in acids is noted from case to case, and in experimental hemosiderosis, with the mode of its production. The age of the pigment appears to have little influence on its speed of solution. The size of the granule has a material influence on the speed of solution, coarser granules resisting longer.

From Author's Discussion.

METABOLISM OF LACTIC ACID IN DIPHTHERITIC TOXEMIA. C. R. DAWSON and E. HOLMES, Brit. J. Exper. Path. **20**:357, 1939.

Dawson and Holmes, using intact animals, confirm earlier findings that in diphtheritic toxemia there is a failure in the power of the liver to store glycogen with no corresponding failure in the formation of carbohydrate from noncarbohydrate sources. They show also a diminution in the power to remove lactate from the blood stream when this substance is injected intravenously. They demonstrate a partial restoration of the power of the liver to form glycogen after massive doses of an extract of adrenal cortex.

CHEMISTRY OF MOLLUSCUM INCLUSION BODY. C. E. VAN ROOYEN, J. Path. & Bact. **49**:345, 1939.

The chemical reactions of the outer covering of the molluscum contagiosum inclusion body have been investigated. Tests with compound solution of iodine (Lugol's solution) indicate that this envelope is mainly composed of carbohydrate, which can be largely removed by preliminary digestion with fresh human saliva but not boiled saliva. After microincineration the outer covering of the molluscous body is found completely burnt off. The mineral residue of the incinerated inclusion is probably mainly derived from the elementary bodies, but some may possibly come from the matrix in which they are embedded.

FROM AUTHOR'S SUMMARY.

TOXICITY OF ALKYL THIOCYANATES. G. R. CAMERON, C. R. DONIGER and A. W. MCK. HUGHES, J. Path. & Bact. **49**:363, 1939.

Toxicity experiments with laurylthiocyanate and n-butyl-carbitol-thiocyanate (in the form of lethane 384) have been carried out on mice, rats, guinea pigs and rabbits. The methods of exposure included contact in miniature houses sprayed with the undiluted and diluted liquids, cutaneous application, and intravenous, intraperitoneal, oral and subcutaneous administration. Histologic examinations have been made of the organs and blood at various stages of exposure. Undiluted lauryl thiocyanate produces a severe local cutaneous reaction. It is fatal to the experimental animal only when introduced into the body in fairly large amounts. Death is due to respiratory failure, probably of medullary origin. No characteristic effects are produced in the organs and blood. Dilutions of lauryl thiocyanate similar to those used in field work have produced no ill effects. Undiluted n-butyl-carbitol-thiocyanate (lethane 384) produces only a slight local reaction but is fatal to experimental animals in much smaller quantities than is lauryl thiocyanate. Death is due to respiratory failure, probably medullary in origin, and there are no characteristic changes in the organs or blood. Dilutions of lethane similar to those used in field work have produced no ill effects. The authors are of the opinion that both lauryl thiocyanate and n-butyl-carbitol-thiocyanate (as lethane 384), provided they are well diluted, are not likely to be dangerous to human beings who come into contact with them during disinfestation. They emphasize the need for protection of the skin when the undiluted liquids are being handled.

FROM AUTHORS' SUMMARY.

Microbiology and Parasitology

PATHOGENICITY FOR GUINEA PIGS OF TUBERCLE BACILLI IN GASTRIC MUCIN. M. A. MILLS and C. A. COLWELL, Am. Rev. Tuberc. **40**:109, 1939.

Varying doses of tubercle bacilli were injected subcutaneously into guinea pigs, equal numbers of the animals receiving bacilli suspended in mucin and in saline solution, for the purpose of determining whether or not any alterations of pathogenicity would occur with the organisms suspended in mucin. No significant

differences could be noted except that, of the guinea pigs receiving the smallest doses, those given mucinous suspensions showed larger local lesions, which had a greater tendency to ulcerate and discharge their contents. The injected mucin, because of its viscosity, may act temporarily in maintaining a high concentration of bacilli at the site of injection, thus promoting the development of a more extensive local lesion. With the gradual disappearance of the mucin, the infection progresses similarly to that seen in guinea pigs given the saline suspension.

H. J. CORPER.

OXYGEN TENSION AND THE TUBERCLE BACILLUS. W. KEMPNER, Am. Rev. Tuberc. **40**:157, 1939.

The respiratory metabolism of fifteen to twenty day old cultures of the tubercle bacillus H 37 was measured manometrically by the Warburg methods in eightieth-molar glycerin–fiftieth-molar phosphate (p_H 7.4) at fourteen different concentrations of oxygen between 0.1 and 100 per cent of 1 atmosphere (oxygen partial pressures of 0.76 and 7.60 mm. of mercury). Contrary to the "all or nothing theory" of cellular respiration, the respiration of tubercle bacilli was found to be highly dependent on variations in the concentration of oxygen, especially at those concentrations that occur in the body. At an oxygen concentration of 8 volumes per cent the respiration was inhibited by 20.4 per cent, at 2 volumes per cent by 58 per cent and at 1.1 volume per cent by 70 per cent. The oxygen saturation curve of the oxygen transferring ferment of respiration in the tubercle bacillus is very similar in shape to that found for the pneumococcus and to the dissociation curves found for oxyhemoglobin. The respiratory quotient of the tubercle bacillus remained constant for all oxygen tensions applied. Since the oxidative metabolism is practically the only source of energy for the tubercle bacillus, the direct inhibitory influence of a low concentration of oxygen on its respiration will cause "starvation," impairment of the chemical reactions and therefore a decrease of the injurious effects of the bacillus. The beneficial effect of various forms of treatment (high altitude, pneumothorax, phrenic paralysis, thoracoplasty) is discussed on the basis of this finding.

H. J. CORPER.

MEGALOMORPHIC PHASE OF BACTERIA. J. G. WAHLIN and P. J. ALMADEN, J. Infect. Dis. **65**:147, 1939.

The existence of large forms of bacteria, previously reported by various investigators, has been confirmed. Because of the large size of these structures the term "megalomorphs" has been used to designate them.

Megalomorphism has been studied in the following species: Eberthella typhosa; Shigella paradysenteriae, Flexner and Sonne strains; Salmonella paratyphi; Salmonella schottmülleri; Brucella abortus; Brucella suis; Alkaligenes faecalis; Escherichia communior; Aerobacter aerogenes; Aerobacter oxytocum; Klebsiella pneumoniae; Klebsiella ozaenae; Serratia marcescens.

In all the cultures studied the development of megalomorphs was preceded by filament formation characteristic of the R phase. In many instances a reversion to the S form occurred.

The mode of origin of the megalomorph varies, and the variations give rise to several types of structure.

The megalomorph is not an involution form but represents a stage in the life cycle of the bacterium.

FROM AUTHORS' SUMMARY.

PANTOTHENIC ACID AND THE GROWTH OF STREPTOCOCCUS HAEMOLYTICUS. H. MCILWAIN, Brit. J. Exper. Path. **20**:330, 1939.

McIlwain has shown that pantothenic acid is necessary for growth of Streptococcus haemolyticus. This substance, which is an amide of a dihydroxyvaleric acid and beta alanine, was first characterized as a nutrient for yeast by R. J.

Williams in 1933. Since then it has been implicated in the nutrition of certain bacteria, of the chick and of the rat. This work is a further instance of the wide applicability of nutritional studies in a restricted field.

GLUTAMINE AND THE GROWTH OF BACTERIA. P. FILDES and G. P. GLADSTONE, Brit. J. Exper. Path. **20**:334, 1939.

Fildes and Gladstone confirm the finding of McIlwain and his collaborators that glutamine is an essential factor for growth of Streptococcus haemolyticus. It functions in vitamin-like concentrations. The general conclusions of the authors suggest that glutamine has a wider nutritional significance than as a factor for growth of streptococci and that its dispensability or otherwise as a nutrient depends on the powers of synthesis of the bacteria tested.

Immunology

PREPARATION OF DIPHTHERIA ANTITOXIN IN A STATE OF HIGH PURITY. C. G. POPE and M. HEALEY, Brit. J. Exper. Path. **20**:213, 1939.

Pope and Healey have used diphtheria antitoxin which has already been purified by enzyme methods as the starting material in an attempt to secure pure antitoxin. After specific precipitation of the antitoxin by toxin, the toxin in the precipitate was destroyed with pepsin and the liberated antitoxin purified. The product obtained was completely precipitable with toxin and appeared to be free from other antibodies to Corynebacterium diphtheriae.

STUDIES ON BACILLUS PESTIS ANTIGENS AS PROPHYLACTIC AGENTS. H. SCHÜTZE, Brit. J. Exper. Path. **20**:235, 1939.

It has always been assumed in prophylaxis against bubonic plague that a highly virulent, smooth organism was necessary for the preparation of the vaccine. Schütze, using rats and mice, found no correlation between the prophylactic efficiency of a vaccine and the virulence and colonial smoothness of the culture from which it was obtained. On the other hand, the amount of envelope antigen was highly important in the rat, but much less so in the mouse.

THE ANTIGENIC PROPERTIES OF STREPTOLYSIN. N. W. ABDALLA and J. W. MCLEOD, Brit. J. Exper. Path. **20**:245, 1939.

Abdalla and McLeod prepared a stable form of streptococcic "serum-free" hemolytic filtrate by using as medium an extract of meat prepared at a temperature below 75 C. They confirmed the work of Todd in finding that such a filtrate was actively antigenic and lethal for the rabbit; they differed from him in finding that filtrates containing horse serum did not produce antibody against "serum-free" hemolysin, although these filtrates immunized rabbits against a lethal dose of "serum-free" hemolysin. Rabbit serum hemolytic filtrates produced both antilytic and protective antibodies against "serum-free" hemolysin.

PSEUDOLYMPHOCYTIC CHORIOMENINGITIS. F. O. MACCALLUM, G. M. FINDLAY and T. M. SCOTT, Brit. J. Exper. Path. **20**:260, 1939.

MacCallum, Findlay and Scott describe a new virus. Two strains have been isolated in mice inoculated with the cerebrospinal fluids of 2 patients who had symptoms of benign aseptic lymphocytic meningitis. The disease in mice is very similar to that produced by the virus of lymphocytic choriomeningitis, but there is no apparent relation between the two viruses. The question whether the virus is of human or of murine origin requires further observation.

PROPERTIES OF ANTIGENIC PREPARATIONS FROM BRUCELLA MELITENSIS. A. A. MILES and N. W. PIRIE, Brit. J. Exper. Path. **20**:278, 1939.

Miles and Pirie continue the description of the antigen from Brucella melitensis. The third part of the study is concerned with the preliminary results of hydrolysis and with the biologic properties of the antigen and of its breakdown products. The simplest material that will still precipitate with antiserum at high dilution is a complex of a phospholipoid and the nitrogen-formyl derivative of an amino polyhydroxy substance; this complex also contains a small amount of phosphate readily removable by hydrolysis. The native antigen is less toxic and more antigenic than the partly broken-down materials.

PURIFICATION OF DIPHTHERIA TOXOID. C. G. POPE and F. V. LINGGOOD, Brit. J. Exper. Path. **20**:297, 1939.

Pope and Linggood have investigated the ratio of the theoretic toxin nitrogen to the coagulable nitrogen found in a number of crude diphtheria toxins and toxoids and have shown the presence of a large amount of coagulable protein other than toxin protein in such products. By using a special medium of low nitrogen content they have been able to reduce the amount of this contaminating protein, which can be almost completely eliminated from the resulting toxoids by treatment with charcoal. From such charcoal filtrates it has been found possible to secure toxoids of a purity of 1,500 Lf units per milligram of nitrogen by simple methods involving no acid precipitation.

CLOSTRIDIUM SORDELLII TOXIN. L. E. WALBUM and G. C. REYMANN, J. Path. & Bact. **49**:185, 1939.

The production of this toxin was largest in peptone broth without the addition of dextrose. Bacillus coli–fermented broth was a less suitable medium. Additions of peptone exceeding about 1 to 2 per cent appeared to impair the production of toxin. In broth containing pieces of meat, toxin production was less than in ordinary peptone broth. Witte peptone has proved to be particularly suitable. Clostridium sordellii toxin has its maximum point of stability in the neighborhood of p_H 6.0. The optimum reaction for the albumose-digesting enzyme lies around p_H 7.0. The gelatin-liquefying enzyme has its action optimum at about p_H 6.5. Tables show the results of the series of investigations made by Walbum and Reymann on the conditions under which the production of toxin occurs in cultures of the five most important gas gangrene bacteria.

FROM AUTHORS' SUMMARY.

Tumors

ARGENTAFFINE TUMORS. J. E. PORTER and C. S. WHELAN, Am. J. Cancer **36**:343, 1939.

A series of 84 argentaffine tumors is reported. Three of these, arising in the small intestine, were malignant. Eighteen malignant argentaffine tumors not previously tabulated have been discovered recorded in the literature, bringing the number to 64, excluding the 3 described here. Argentaffinomas are encountered in from 0.2 to 0.5 per cent of appendixes that have been surgically removed. The incidence of the tumors in the small bowel is less than one-half that of carcinoids in the appendix. The former have a predilection for the terminal part of the ileum, tend to cause obstruction and not infrequently metastasize. All argentaffinomas are potentially malignant. Their grade of malignancy as a rule is low. Treatment is surgical. The function of the argentaffine cell is not known; its origin is probably from the endoderm. It is suggested that argentaffinomas found in obliterated appendixes may be the result of proliferation of the argentaffine cells following chronic inflammation, while the tumors of extra-appendical origin are true neoplasms.

FROM AUTHORS' SUMMARY.

GENETICS OF NON-EPITHELIAL TUMORS IN MICE. C. C. LITTLE, W. S. MURRAY and A. M. CLOUDMAN, Am. J. Cancer **36**:431, 1939.

The genetics of nonepithelial tumors in mice is not the same as that of mammary tumors. No simple mendelian phenomena are discernible. If any type of mendelism is involved, it includes multiple factors and a marked influence of the internal environment. In the determination of the absolute incidence of nonepithelial tumors among hybrid animals, there seems to be, in the material observed, approximately equal influence from male and female parents. In the determination of the type of nonepithelial tumor, i. e., the type of tissue and cell affected, there is some slight indication that the maternal ancestor may be more influential. The determination of the location of the nonepithelial tumor in the hybrid appears to be equally affected by each parent. The great increase in the incidence of uterine sarcoma and in that of nonepithelial tumor of the mammary region among hybrids suggests the possibility that an imbalance of ovarian and/or some other endocrine function may be an important etiologic factor in the development of these tumors. Preliminary evidence suggests that a possible relationship may exist between dilute pigmentation and increased formation of nonepithelial tumors. This, if confirmed by more extensive data, would probably be an indication of some physiologic factor rather than of anything in the nature of genetic linkage.

FROM AUTHORS' CONCLUSIONS.

THE BLUE NEVUS. F. MONTGOMERY and J. E. KAHLER, Am. J. Cancer **36**:527, 1939.

Sixty-five blue nevi occurring in 62 patients are recorded. Thirty-eight of the lesions were studied histologically. It is the belief of the authors that if blue nevi are looked for, they will be found much more frequently than the literature would indicate, and that they are of relatively common occurrence. The onset in infancy or in early childhood of a firm blue to blue-gray papule or nodule which remains such, without increase in size, usually permits a clinical diagnosis of blue nevus. The histologic picture is characteristic, although occasional cases are found in which ordinary pigmented nevus cells are found in the same lesion. The blue nevus rarely shows malignant change. When this occurs, it seems to be that of a relatively slow-growing melanosarcoma. Like ordinary pigmented nevi, the blue nevus usually runs a benign course, and there is no need for surgical excision unless for cosmetic purposes or unless the lesion is situated in an area exposed to repeated trauma, friction or irritation. The problem of the mesodermal or epidermal origin of these tumors is discussed. The blue nevus is differentiated from various conditions, especially from melanoepithelioma, with which it has been confused clinically and even pathologically. Occasionally a blue nevus may show increase in size or present a steel blue color simulating that of a melanoepithelioma. In such instances wide and deep surgical excision is indicated.

FROM AUTHORS' SUMMARY.

THE VASCULAR PATTERN OF CERTAIN INTRACRANIAL NEOPLASMS. A. L. SAHS and L. ALEXANDER, Arch. Neurol. & Psychiat. **42**:44, 1939.

Sahs and Alexander studied the vascular pattern of 23 brain tumors (meningioma, various type of glioma, papilloma of the choroid plexus and metastatic carcinoma of the brain), using the benzidine technic. They conclude that this pattern varies according to the type of the tumor. It is sometimes so characteristic that it may suggest the histologic type of the tumor. For instance, "shrub" and "wind swept tree" formations of blood vessels suggest polar spongioblastoma; a relative paucity of true capillary channels is suggestive of spongioblastoma and astrocytoma; in oligodendroglioma, capillaries are abundant, while in psammoma

and medulloblastoma the centers of the tumors are relatively poor in blood vessels. The common feature was "an appearance suggestive of inadequacy and awkwardness of circulation as compared with that of normal brain tissue."

GEORGE B. HASSIN.

ASPIRATION BIOPSY OF TUMOR OF THE LUNG. L. F. CRAVER and J. S. BINKLEY, J. Thoracic Surg. **8**:436, 1939.

Aspiration biopsy of tumor of the lung is a valuable and relatively safe diagnostic procedure in selected cases. Pathologists familiar with the appearance of the stained smears can make a diagnosis if tumor tissue is obtained. There is a substantial percentage of cases of early primary cancer of the lung in which bronchoscopic inspection will fail as a diagnostic procedure.

FROM AUTHORS' CONCLUSIONS.

INFLUENCE OF TRANSPLANTED NORMAL TISSUE ON BREAST CANCER RATIOS IN MICE. J. J. BITTNER, Pub. Health Rep. **54**:1827, 1939.

By inoculating normal tissue from young female mice of a stock with a high incidence of cancer, an influence may be transmitted which produces results similar to those of the "breast cancer producing influence" normally obtained in the milk while nursing.

FROM AUTHOR'S SUMMARY.

EXPERIMENTAL LUNG CANCER. H. A. MAGNUS, J. Path. & Bact. **49**:21, 1939.

In a series of market mice with an incidence of tumor of the lung of from 4 to 8 per cent, multiple bronchial papilloma were produced in 95.2 per cent by the introduction into the stomach of a suspension of 1,2,5,6-dibenzanthracene in olive oil. It is highly probable that aspiration of minute quantities of the carcinogenic agent accounts for the production of these tumors. In 75 per cent of the affected mice the bronchial papilloma showed clear evidence of malignancy, with metastasis in 2 mice. The morbid anatomy of spontaneous and of artificially induced pulmonary tumors in mice is the same. If the material introduced did in fact reach the lungs by aspiration, the smallness of the dose of 1,2,5,6-dibenzanthracene required to produce tumor of the lung in the mouse is emphasized.

FROM AUTHOR'S SUMMARY.

RELATION OF ADRENAL TUMORS TO VASCULAR CHANGES. J. HOFFMEYER, Virchows Arch. f. path. Anat. **302**:627, 1938.

A man aged 25 years who had hypertension and retinal arteriosclerotic changes died of cerebral hemorrhage. Necropsy revealed a large chromaffin tumor of the left adrenal and marked arteriosclerosis with lipoid infiltration. A woman dying at the age of 93 years had a small cortical adenoma of the adrenal. Arteriosclerotic changes were slight, not in accord with the advanced age of the subject, and there was a minimal degree of lipoid infiltration of the vessels. The first case is interpreted as one of medullary hyperfunction with hyperadrenalinemia and cortical hypofunction; the second, as cortical hyperfunction. The arteriosclerotic manifestations in the first case were ascribed to hyperadrenalinemia. But since the cortical hypofunction was associated with marked lipoidosis, whereas in the second case cortical hyperfunction was associated with very slight lipoidosis, the adrenal cortex is held to play a role in lipoid metabolism.

O. T. SCHULTZ.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

JEFFERSON H. CLARK, *President*

H. L. RATCLIFFE, *Secretary*

Regular Meeting, Nov. 10, 1939

Epithelial Tumors of the Bladder. J. E. ASH, Lieutenant-Colonel, Medical Corps, United States Army (by invitation).

Included in the American Registry of Pathology, which is sponsored by the National Research Council and maintained at the United States Army Medical Museum, is the registry for bladder tumors, of the American Urological Association. There are at present over 3,200 cases entered in this particular registry, and these form the basis for this presentation.

Clinically, there have been over three times as many males as females affected with this type of tumor. Over 60 per cent of the patients were in the 50 to 60 year age groups, the youngest patient was 17 at onset, and the oldest, 105 at death. The initial symptom in about 75 per cent of the patients was hematuria, with which dysuria was frequently associated. The condition has developed in 75 aniline workers. In 2 persons it was secondary to schistosoma infestation. There has been no significant association with calculi or previous infection.

The epithelial tumors are predominantly transitional cell, and over two thirds of them are primarily papillary. Adenocarcinoma is rare. At the registry we call all papillary tumors "carcinoma, papillary, grade I, II, III or IV," avoiding the use of the term "papilloma." This is not because we fail to recognize the fact that some of the papillary tumors are benign but because it has been our experience that the benign development is not predictable from a histologic examination. There is one group of 93 tumors that were diagnosed elsewhere as papilloma; 33 of the patients have died with tumor or are living with persistence of tumor and 17 have become carcinomatous. The "benign papillomas" are called carcinoma, papillary, grade I; grade II are those in which there is histologic evidence of invasion or in which there is disarrangement, pleomorphism or an unusual number of mitoses, and grades III and IV are those of greater degrees of malignancy, following roughly Broders' index. The papillary tumors are perhaps more consistent in their appearance, even when they are multiple, than are tumors generally, but it is also true that there may be striking variation in different parts of the same tumor. The papillary feature and the transitional character of the cell will frequently be retained in mestastases. As carcinomas go, those of the bladder are not particularly malignant; only about 10 per cent of the primary infiltrating squamous cell tumors have metastasized, and about 7.5 per cent of the papillary ones. Both of these figures include those that are the wildest in histologic appearance and those that are the most widespread in their infiltration. The great majority of the tumors are located in the trigon and about the ureteral and urethral orifices. This fact and the persistence with which the tumors "recur" make them clinically anything but simple. The patients die not so frequently *of* tumor as *with* tumor, the result of infection or of obstruction of the urinary tract. The term "recurrence" is used loosely, for the papillary tumor seldom recurs at the site of removal. The tumor that the clinician encounters after he has operated is a new tumor, not a recurrent or a

metastatic one. The mucosa of the bladder possesses, to an exaggerated degree, the "tumor tendency" of mucosae generally. This diathesis is not confined to the mucosa of the bladder. We have 17 specimens in which the ureter is involved and a number in which the renal pelvis is also involved. The clinician's difficulty is not in being able to eradicate the primary papilloma but in removing it in such a way that he does not do more damage to the vital physiologic region than the tumor. The fact that new tumors appear is not necessarily a reflection on his skill.

Histologically, there is great variation in cell character. Colonel Dart was able to identify 16 definite types, but on a careful correlation of the clinical data he has been unable to attach any prognostic significance to this classification. The normally transitional epithelium shows a striking tendency when it has accumulated in masses, either on the villi or after infiltration of the wall of the bladder, to metamorphose either to the squamous or to the glandular type, so that it is not uncommon to find in the same field foci of squamotoid and adenomatoid cells. My colleagues and I look on the former as an especially bad sign. It is not infrequent to find a remarkable sarcomatoid anaplasia of the infiltrating cells, a finding that is difficult to differentiate from true sarcoma. In fact, it is very likely that there are cases in which there is a simultaneous sarcomatous change in the stroma of the primary carcinoma. The papilloma is really a fibroepithelial and not a purely epithelial tumor.

There are several interesting incidental histologic pictures. The most frequent is that of lymphatic follicles in the submucosa, the so-called "follicular cystitis" of the urologist. Cysts developing in Brunn's follicles and little gland accumulations in the superficial submucosa, the "cystitis cystica and glandularis" of the urologist, and bullous edema, another clinical entity, are common. The latter is a polypoid hyperplasia of the mucosa comparable to that in the nose and accessory sinuses.

The prognosis is generally not good. Of 2,500 patients on whom we have records, 1,380 have died—46 of them with tumor five years or more after their initial treatment. The average case might be summarized as follows: The patient is a white man aged 60 years. The chief complaints are hematuria and dysuria. Cystoscopic examination shows a single papillary tumor located on the posterior surface of the base of the bladder. The pathologic diagnosis is carcinoma, papillary, grade I or II. The prognosis is: repeated recurrence in spite of treatment and about 1 chance in 3 of living five years and about 1 chance in 25 of complete recovery.

JEFFERSON H. CLARK, *President*

H. L. RATCLIFFE, *Secretary*

Regular Meeting, Dec. 14, 1939

Annual Gross Lecture: Cardiovascular Reactions in Glomerular Nephritis.
WARFIELD T. LONGCOPE.

A study of glomerular nephritis which has been in progress in the medical clinic of Johns Hopkins Hospital for about fifteen years has shown that the cardiovascular system is affected in one way or another from the earliest to the latest stages of the disease.

In the acute phase the abrupt rise in blood pressure is one of the characteristic symptoms and signs. In certain respects the vascular reactions of patients with glomerular nephritis differ from those of persons suffering from chronic hypertension. Acute myocardial failure is a common accompaniment of the hypertension

in these patients. Dyspnea is frequent, there is a temporary increase in the size of the heart, systolic murmurs occur, and in the severe cases a gallop rhythm appears. There are increase in venous pressure, enlargement of the liver and edema. The sudden appearance of pulmonary or cerebral edema may prove fatal. The electrocardiogram may show transient alterations, suggesting interference with the arterial circulation in the myocardium.

The peripheral vessels may be affected even in the earliest stages of the disease. Retinal hemorrhages are not uncommon; retinitis with exudates or choroiditis is rare. It has been supposed for many years that the peculiar edema of acute glomerular nephritis is in part due to widespread injury of capillaries and minute blood vessels. There has been, however, little anatomic evidence to support this view. Careful search, nevertheless, will disclose acute necrosis and hyaline degeneration of scattered arterioles, not only in the kidneys but in many organs of the body from patients who die during the first few weeks of the disease.

It seems most probable that these acute changes in the cardiovascular system are closely connected with the factor or factors that cause the nephritis. An infection, often of the tonsils and pharyngeal ring or of the skin, precedes with great regularity the onset of acute glomerular nephritis. These infections are usually due to hemolytic streptococci, but they may be caused by other organisms. Subacute gonococcic endocarditis, for instance, is especially prone to be complicated by typical diffuse glomerular nephritis.

The nephritis which may be associated with one or another of these infections is by no means caused by an actual invasion of the kidney by bacteria but seems to be the result of some form of allergic reaction to the infection, which involves not only the kidneys but many parts of the cardiovascular system. The nearest approach to the appearance of the human disease produced experimentally has been accomplished by the intravenous injection into rabbits of nephrotoxic serum prepared according to the method of Masugi. In the experimental production of the disease an antigen-antibody reaction appears to take place in the renal tissues, which results in acute nephritis.

Once the disease is initiated, it may run one of several courses. Recovery takes place in a fair number of adults and is common in children. Some patients recover symptomatically, but the disease persists for years in a quiescent form. In others the progress is continuous, reaching a subacute, then a chronic, and finally a terminal stage within months or a few years. In others a chronic stage with exacerbations supervenes. This may continue for years before the terminal stage sets in.

During the chronic and slow advance of the disease the blood pressure may be within normal limits or only moderately elevated. One peculiarity often noticed with the advent of the terminal phase is a pronounced rise in blood pressure. This may be as prominent a feature as the rise in blood pressure in the nephritis of malignant hypertension. Autopsy in this group of cases of glomerular nephritis is especially likely to show advanced lesions in the vascular tree of the kidneys and of other organs. Rarely there is narrowing of the main renal arteries or of their large branches; more commonly the intrarenal arteries show proliferative endarteritis or the capillaries marked hyaline degeneration. There may be, in addition, medial thickening.

One might suggest that the terminal stage with the frequent accompaniment of marked hypertension and other distinctive features is dependent in part, if not largely, on rapidly advancing disease of the arteries or arterioles. Why these lesions in the arteries and arterioles should occur is another question which cannot be answered at present with any certainty.

Even more obscure is the mechanism by which the various forms of injury to the kidney which I have described are connected with the elevation in blood

pressure. The work which is now proceeding with such interesting results on "renin," on the loss of an inhibitor, on the presence of an excitor and on tachyphylaxis may, it is hoped, eventually throw light on the subject.

In conclusion I may say that I have tried to trace the part which the cardiovascular system plays in the natural history of glomerular nephritis or hemorrhagic Bright's disease. The upshot of these studies is that this system is affected in one way or another throughout the course of this disease. During the acute phase, which may be interpreted as the outcome of an allergic reaction to infection, the heart bears the brunt of the injury, and its failure is often the immediate cause of death. In the quiescent and prolonged chronic stage, disease of the vascular system falls into the background to become prominent again in the terminal stage, when progressive disease of the renal arteries and arterioles precipitates renal failure and death.

NEW ENGLAND PATHOLOGICAL SOCIETY

SIDNEY FARBER, *President*

BENJAMIN CASTLEMAN, *Secretary*

Regular Monthly Meeting, Nov. 16, 1939

Relationship of Flocculating Antibodies to Tissue Hypersensitiveness and Localized Disease. PAUL R. CANNON, Chicago (by invitation).

The enhanced ability to localize infectious agents is one of the outstanding properties of immune tissues, but the mechanisms responsible are not clearly understood. Much emphasis has been placed on the significance of the intensified inflammatory reaction in the localizing process. Less attention has been paid to the role of flocculating immune bodies (agglutinins and precipitins). Accumulating evidence indicates, however, that these antibodies are of primary importance in promoting antigenic localization, both in the tissues and in the blood stream. There is but little question that in the body specific antibodies do combine quickly with antigen, thereby facilitating the prompt localization of antigenic particles in the tissues or their speedy removal from the circulating blood.

If one assumes that this union of antigen and antibody in tissues serves a useful function, the question arises what the general function of antibodies may be. Zinsser has suggested that they arise because of the presence in tissues of foreign, nondiffusible colloids which, in order that they may be utilized or excreted, must be broken down into diffusible forms. Wells, furthermore, has advanced the postulate that the antibody mechanism in this way serves to maintain the specificity of the body's proteins by initiating the disintegration of foreign proteins into amino acids before their absorption. According to these views, antibody action may be regarded as part of the process of parenteral digestion. The prevailing opinion is that in the antigen-antibody union, specific antibody globulin becomes deposited on the surface of an antigenic particle, thereby increasing the cohesiveness and viscosity of the antigenic surface. The process is essentially an aggregative or coagulative one and may be compared with that produced by rennin in the earliest stages of gastric digestion. The flocculating antibodies, therefore, may initiate the conversion of foreign colloids into simpler, more assimilable forms; the subsequent manifestations of the antigen-antibody combination may represent progressive phases of colloidal dispersion (lysis, intracellular digestion) as they occur outside of or within cells.

The experiments of Opie have done much to clarify the problem of the significance of precipitins in antigenic localization. Because of the relationship of this phenomenon to other types of allergic lesions, a clearer understanding of its

mechanism is urgently needed. Opie concluded that the Arthus reaction occurred because of the union within the tissues of antigen and antibody and that there is marked parallelism between the rise and fall of precipitin in the blood and the variations in intensity of the cutaneous reactivity on injection of the specific protein. Other experienced workers have failed to observe this relationship, and some, indeed, have concluded that there is no relationship between precipitins and tissue hypersensitiveness.

These opposing views naturally suggest the possibility that the difference in experimental findings may be due to the fact that differing methods were employed. Current methods for the determination of the precipitative strength of an antiserum are defective in that the so-called titer is obtained by dilution of the antigen rather than of the antibody. Experiments which Marshall and I have made indicate that, by the use of the agglutination of collodion particles to which a specific protein has been adsorbed, exact titers of antibody can be determined by the usual serologic procedure of serial dilution of the antibody. In this way the precipitative potency of the serum can be obtained and compared with the skin reactivity to the particular protein. Experiments by this method indicate a precise correlation between the precipitative strength of a serum and the intensity of cutaneous hypersensitiveness to that protein.

These experiments do not exclude the possibility that precipitins may exist in local tissues, where they may combine with antigen in the absence of detectable antibodies in the circulating blood. They merely furnish evidence that in one well known type of tissue hypersensitiveness the reaction occurs only when precipitins are present in the blood and tissues and suggest, as Opie had concluded, that precipitate, within or between cells, is responsible for the development of the Arthus phenomenon.

Experiments of Blacklock, Gordon and Fine, and of Taliaferro and Sarles, furnish evidence, furthermore, that precipitins may play an important part in the localization of living antigen. These workers have shown that immunity to reinfection with certain parasitic larvae is accompanied by a precipitative phenomenon whereby the digestive tracts of the larvae become plugged by a precipitate. As a result, the larvae become immobilized and stunted in their growth and are surrounded by inflammatory cells. The latter workers have shown that this localizing mechanism can be demonstrated by passive transfer of serum into normal animals from resistant ones. Localized granulomatous lesions resulted, and but little migration of parasites occurred. These experiments offer further confirmation of the view that flocculating antibodies may play an important part in the localization of infectious agents.

Similarly, agglutinins have been shown to be important agents in the localization of bacteria near the portals of entry. This effect can be observed best in subcutaneous tissues, where the sluggish flow of tissue fluids facilitates adherence of antibody-coated micro-organisms to the tissues and to one another. Here, too, the intensified local inflammatory reaction accompanies and promotes the continuous localization of the infectious agents. This flocculative reaction has been shown to occur also with pneumococci in the sputum of patients given specific antipneumococcic serum; later, agglutination is followed by a more effective phagocytosis of the pneumococci.

It is possible that too much emphasis has been placed on the adverse effects of the localized lesions of hypersensitiveness. The harmful manifestations may be looked on as essentially toxicologic by-products of a reaction that is fundamentally beneficent. It is not surprising that antigenic stimuli which when minimal cause only insignificant tissue reactions can, in an exaggerated form, lead to profound cellular damage. This does not mean necessarily that the mechanism itself is at fault. It may mean only that a biologic process which is generally beneficial in maintaining the integrity of the body's proteins may under certain conditions be harmful to the individual.

DISCUSSION

VALY MENKIN: The earlier studies of Rössle and particularly those of Opie in the early twenties have contributed considerably toward the present understanding of local anaphylaxis or allergic inflammation. One has in this reaction an exaggerated specific response on the part of the host tending to eliminate ultimately the homologous foreign protein. The nonspecific inflammatory reaction represents a peculiar adaptation in the vertebrate kingdom whereby a foreign body is first localized at its point of entry and finally eliminated. Precisely the same mechanism enters into play in an animal hypersensitized or immunized to a foreign protein, but with this difference: the reaction is now exaggerated in intensity and its rate of development is accelerated. This fact promotes both more rapid localization and ultimate disposal. This is, in part at least, brought about by the additional presence of immune bodies, which are absent in the nonspecific inflammatory reaction. The fundamental work of Opie, the studies of Dr. Cannon and the observations of Rich and of others support this view.

Opie believed that there was some degree of parallelism between the intensity of the Arthus phenomenon and the precipitin titer of the serum. By his technic, whereby the antigen was diluted, he could not demonstrate an exact parallelism. It is true that there would be some difficulty in demonstrating an exact correlation between the intensity of a skin reaction and the titer of an antibody in the blood serum. It is perfectly conceivable that the titer of precipitin in the tissue may be somewhat different from that of precipitin in the serum. These various difficulties have now been overcome by Dr. Cannon with his new technic. This is a real advance. What we originally surmised, namely, that there is some sort of parallelism between the intensity of the Arthus phenomenon and the titer of precipitin in the serum, seems now a demonstrated fact.

There are some additional points of interest which might be brought out:

1. The intensity of an anaphylactic inflammation is paralleled by the precipitin titer. Opie has pointed out that the antigen is fixed at the site of entry. Would the precipitin titer or the intensity of the anaphylactic inflammation likewise determine the degree of fixation of nonrelated substances? In other words, would dyes, lethal metals, other proteins or bacteria be equally retained at the site of a specific Arthus inflammation? This would be of distinct interest, for Opie originally viewed the fixation of the antigen as largely the result of specific precipitation of antigen and antibody in the tissue spaces. Several years later, when working in Opie's laboratory, I had occasion to demonstrate that foreign proteins would be retained in situ by any acute nonspecific inflammation, such as that caused by aleuronat or that caused by Staphylococcus aureus. On the basis of this, I expressed, at the time, the opinion that the primary mechanism of fixation in the Arthus phenomenon is probably the local inflammation per se. Later this fixation was shown to be primarily referable to the establishment of an effective lymphatic blockade. Nevertheless, the specific precipitation caused by the meeting of antigen and antibody doubtless plays an important part in reenforcing or intensifying the primary mechanism of fixation. This would follow by the formation of a larger colloidal aggregate which would thus not readily diffuse through occluded lymphatics.

It is perhaps fully apropos to point out that years before the mechanism of fixation was described, Opie, wholly unaware of this mechanism, though he carefully described the histologic picture presented by the anaphylactic inflammation, pointed out, among other facts, the large number of thrombosed lymphatics and the network of fibrin found in the lesion. These are the primary elements essential for an active fixation. It is to be recalled that in the guinea pig the allergic inflammation in an area of tuberculous reinfection, known as the Koch phenomenon, fixes the bacilli precisely by this mechanism of fibrinous occlusion, as Lurie has recently shown, and apparently not by the intermediary presence of antibodies.

2. This brings me to the final point. Several years ago, my associates and I were able to show that fixation at the site of inflammation could be inhibited by dissolving the fibrinous barrier with concentrated urea. I therefore wonder whether with each successive cutaneous injection of the protein antigen, during the period of immunization, one could not inject alongside it a solution of concentrated urea. It is conceivable that the lymphatics would thereby be kept open. The antigen might thus be readily absorbed, and the Arthus phenomenon might fail to develop locally. Instead, the contact of antigen and antibody would tend to occur in the systemic circulation or in the visceral organs, with subsequent production of general anaphylaxis. Such an experimental procedure might thus be conducive to the conversion of the usual local anaphylaxis or Arthus phenomenon to a state of generalized anaphylaxis with its disastrous consequences. Such observations might be of value in clarifying the concept of the mechanism of antigenic fixation in the Arthus phenomenon.

TRACY B. MALLORY: When a man is called on to discuss a paper under these conditions, he should, I believe, adopt the role of the person in the ecclesiastical courts known as the devil's advocate. It is his function to point out any trace of the devil's influence that might prevent sanctification. To come down to a more prosaic simile, he must look for the fly in the ointment. I am obviously going to have a hard time playing properly my role as the devil's advocate, because I cannot find much to criticize.

The work of Opie was certainly extremely fundamental and has influenced thinking on problems of allergy and immunity as much as that of any other single worker. His demonstration of the wide parallelism between the intensity of allergy and the strength of the precipitin reaction was most suggestive, and one was tempted to accept it immediately even though absolute parallelism had not been demonstrated. Dr. Opie knew very well, of course, that the ordinary precipitin reaction was not a perfect test to use under the circumstances, and it is comforting to have his work repeated with much more sensitive methods and to find that all that he predicted has actually been demonstrated.

In discussing experimental work carried out entirely on animals one is apt to look at it from three points of view: Is the work itself sound logically and technically? How does it fit into the general pattern of knowledge, and how does it relate to other experiments, particularly those with different species of animals? Finally, since one is a physician, what relation may be inferred to diseases of man? In regard to the intrinsic evidence in this paper, I see no possible reason to question any part of it. The nature of the phenomenon seems to have been demonstrated conclusively. On the question of relation to other known facts of allergy Dr. Cannon has been conservative. Perhaps a little unfairly, I am going to try to read between the lines, to infer what I suspect he believes in the hope that I can tempt him to disagree with me when his opportunity for rebuttal comes. There are two problems in immunology relating to hypersensitivity, on which almost every one is called sooner or later to take a stand. One is the relationship of hypersensitivity to immunity; about that Dr. Cannon has definitely expressed the opinion that local hypersensitivity is an important factor in the protection of the organism as a whole. I think few physicians here in Boston who have been extensively influenced by Dr. Zinsser throughout their careers would fail to agree with him on that point. The other point I hope I can persuade Dr. Cannon to commit himself on is the extent to which he regards the Arthus phenomenon as a prototype of the hypersensitivity reactions. One can often guess almost as much of what a person thinks by what he fails to say as by what he says, and I have made a guess from listening to Dr. Cannon that may be entirely wrong, but, if so, all the better, because he will contradict me. I imagine he probably is following closely Dr. Opie's line of thought that the Arthus phenomenon is representative of at least a majority of the most important allergic reactions. Assuming this, I intend in advance to disagree with him. There are certain points which Dr.

Dienes has repeatedly emphasized, and others which he and I in collaboration believe we demonstrated, which we feel cannot be harmonized with such a point of view. One's thinking on problems of hypersensitivity is unquestionably greatly influenced by what one sees in the particular experimental animals that one works with. Almost no one with experience in experimental hypersensitivity fails to realize that the symptom complex is entirely different for each species of animal. The rabbit readily presents a severe Arthus phenomenon and is a prolific producer of antibodies. The guinea pig can be made to show an Arthus phenomenon only with special technic and is a poor producer of antibodies. On the other hand, this animal can be made highly hypersensitive, and Dr. Dienes and I, at any rate, believe that it may show sensitivity at a time when there are no detectable antibodies in the blood stream. It is possible that we ought to reexamine that question with the technic Dr. Cannon has suggested, but we did not rely wholly on the precipitin reaction. Another excellent method of demonstrating antibodies is that of passive transfer of hypersensitivity. With appropriate technic, there is a period in immunizaton when guinea pigs can be so hypersensitive that they will give intense necrotizing reactions and nevertheless their serum will not transfer the hypersensitivity passively. Finally, I think we have to convict Dr. Cannon of a slight misreading of Dr. Dienes's paper when he lines up Dr. Dienes among those who found parallelism between precipitin reactions and hypersensitivity. It is quite true that in the animals discussed in that paper, which showed marked necrotic reactions of the delayed type, precipitins did develop in high titer, but these did not appear until several days after the skin reactions were observed.

LOUIS DIENES (by invitation): It is my impression that the close parallelism between the intensity of the skin reaction and the amount of antibodies circulating in the blood is a phenomenon more or less peculiar to the rabbit and is not observed as a general rule. Rabbits produce antibodies easily and in abundance whereas the hypersensitiveness of the skin dependent on the active immunity process remains relatively slight. In other animals the active immunity process develops with greater relative intensity and the phenomena connected with free antibodies with less intensity. I have observed many guinea pigs which responded to the injection of a few hundredths of a milligram of egg white with large necrotic skin reactions, but anaphylactic shock could not be produced in them, and their serum did not passively transfer anaphylaxis. Man when treated with small doses of an appropriate antigen, such as rabbit or guinea pig serum, after a few days will show large delayed reactions similar to tuberculin reactions. These reactions, like the previously mentioned reactions of guinea pigs, are not produced by free circulating antibodies but are connected with the development of the active immunity response.

Allergic phenomena fall into two groups according to the characteristics of the reactions and the conditions under which they are observed. One group is always associated with free antibodies and can be reproduced by artificial introduction of antibodies. The skin reactions with small doses of antigen are characterized by quick development and short duration. The other group is produced only by injection or active immunization and shows no connection with free antibodies. The skin reactions even with small doses of antigen are delayed and persistent like tuberculin reactions. The best evidence that such reactions are not produced by free antibodies is that artificial introduction of free antibodies consistently and in different animal species produces different types of reactions. Quantitative variation of the experiment and variation of the nature of the antigen exert no influence in this respect. The observation of small amounts of antibodies in connection with the second group of allergic phenomena is of no importance because neither small nor large doses of free antibodies will produce similar phenomena.

The mechanisms by which these two groups of allergic phenomena are produced are not different in principle, as the active immunity process depends on the production of antibodies in the tissues. But for the understanding of immunity

in the infectious diseases it is of great importance to know that there are immunity phenomena which are produced exclusively by active immunization in situ and are not reproduced by introduction of free antibodies. A large part of immunity phenomena observed during the infectious diseases belong to this group, such as the allergic reactions similar to the tuberculin reaction.

While I am inclined to give a restricted significance to the study of the Arthus phenomenon, the conclusions of Dr. Cannon concerning the importance of agglutinins and precipitins seem to me of great significance. Studies of the immunity phenomena in the living animal and the extension of these studies to all varieties of parasitic organisms, including parasitic worms and insects, will slowly allow the reconstruction of the actual processes going on in the organism during infectious diseases, processes which are at present very imperfectly known.

JOHN E. GORDON (by invitation): Dr. Cannon's observations on the Arthus phenomenon have a direct important clinical relationship. Those who have seen the acute local hypersensitivity that develops after administration of serum are finding support for the views he has expressed, namely, the relationship between time and doses of serum in clinical Arthus reactions.

PAUL R. CANNON: I have focused attention on the flocculative reactions because I believe that too little emphasis has been placed on their relationship to allergc phenomena. A clearer understanding of the mechanism of the Arthus phenomenon should help considerably to clarify some of the uncertainties in the problem of allergic inflammation. This has been delayed, unfortunately, because of technical difficulties.

It is too early to tell whether the Arthus phenomenon is a prototype of allergic reactions in general. Zinsser has stressed the close similarity between anaphylaxis and allergy, despite the many apparent differences. One must not forget that sensitized cells and tissues react in anaphylaxis and allergy to many kinds of colloidal materials which vary tremendously in molecular size and diffusibility. It is possible that precipitation within a cell may occur as a submicroscopic invisible process which, nevertheless, may lead to enough cellular injury to cause local hyperemia and edema. Precipitins in the serum might thus be at too low a concentration to be demonstrated by methods now available.

The relationship between precipitation in vivo and the inflammatory reaction is a problem too complicated to go into now. Two processes apparently develop, the primary antigen-antibody union with the accompanying local injury to cells and the inflammatory reaction to injury, which quickly follows. I have emphasized the importance of the antigen-antibody combination, and Dr. Menkin that of the inflammatory reaction, although we both recognize the mutual importance of the two biologic processes.

I can see no reason to deny the conclusions of Mallory and Dienes with respect to allergic reactions in the absence of demonstrable antibodies in the serum. Aside from technical difficulties, the development locally, within cells, of the antibody-forming mechanism may, as they have suggested, account for the early hypersensitivity of these cells to antigen. But it is also possible that the hypersensitive reaction occurs because of an intracellular precipitative reaction which has not been revealed by available methods.

Aside from its theoretic interest, the Arthus reaction is of practical importance, as Dr. Gordon has emphasized. Several cases of massive necrosis following intramuscular injection of serum have been reported, and Tumpeer and his associates demonstrated the presence of precipitins against horse serum in the serum of a patient who died because of the development of a massive Arthus reaction. Several workers have shown that a therapeutic antiserum, when injected into a patient hypersensitive to the serum, may be poorly absorbed or inadequately utilized, and there is clinical evidence that the therapeutic effectiveness of a serum varies inversely with the severity of the local reaction.

BUFFALO PATHOLOGICAL SOCIETY AND BUFFALO ACADEMY OF MEDICINE, SECTION OF PATHOLOGY

ERNEST WITEBSKY, *President*

SAMUEL SANES, *Secretary*

Joint Meeting, Nov. 22, 1939

Morphologic Variations in Adenocarcinoma of the Uterine Fundus, with Special Reference to the Action of Progestin and a Progestin-Like Hormone Before and After the Menopause. NORMAN W. ELTON.

Oertel's statement that the romantic attributes of lawlessness and malignancy in cancer have inhibited intelligent effort to analyze the significance of morphologic variations in neoplasms seems especially applicable to carcinoma of the uterine fundus. Recently 2 cancers of this type, found in women prior to the menopause, showed morphologic changes characteristic of the follicular and the luteal phase involving adjacent normal endometrium at the same time, with the exception that the cancers in contrast with the normal endometrium showed a lag in the involution of the luteal phase. Fifty cases of carcinoma of the fundus were then reviewed, and it was noted that cyclic changes had been demonstrated, indicating the activity of a progestin-like hormone on the tumors long after the menopause and in the complete absence of any corpus luteum. It is probable that, although carcinoma of this type may not be caused by a hormone, it responds to the influence of one.

Purely statistical studies were also carried out on this series. The patients were divided into two groups: (1) 21 of an average age of 48, in whom the cancers appeared before or during the menopause and who had noted signs and symptoms for periods averaging four months, a group with a relatively low mortality, and (2) 29 whose cancers occurred after the menopause, at an average age of 61, with signs and symptoms averaging a year in duration, a group with a relatively high mortality. In regard to the prognosis it was found that the factors of anaplasia and invasion were the chief determinants; it is definitely concluded that rarely can a reliable prognosis be made without hysterectomy and that statistics based on curettage and irradiation alone are probably fallacious. Carcinoma occurring ten years after bilateral oophorectomy, compound neoplasms, with associated endometrial sarcoma, apparent cure by curettage alone, or by curettage followed only by irradiation, morphologic changes in the presence of granulosa cell tumor of the ovary, and other interesting observations are possible, to judge from the data available in this series. The complete report will be published in the *American Journal of Clinical Pathology*.

Experimental and Clinical Observations on the Action of Sulfanilamide in Meningococcic Meningitis. ERWIN NETER and CARL A. STETTENBENZ.

It is far more difficult to assay the efficacy of sulfanilamide in meningococcic meningitis than in meningitis due to beta hemolytic streptococci, pneumococci or influenza bacilli. The mortality of nontreated patients with the latter conditions is exceedingly high (above 90 per cent) and is largely independent of such factors as age of the patient and virulence of the particular strain. On the other hand, the mortality of patients with meningococcic meningitis varies greatly and may range from 50 to 80 per cent in the non-serum-treated ones and from 10 to 75 per cent in serum-treated ones.

Experimentally, it was shown by Buttle, Gray and Stephenson and by Proom that sulfanilamide reduces the mortality of mice with meningococcic infections. Their findings have since been corroborated (Rosenthal, Bauer and Branham;

Levaditi and Vaisman; Brown; Long and Bliss). In vitro sulfanilamide inhibits the growth of meningococci, as demonstrated by Branham, Maegraith and Vollum. In order to determine whether a similar bacteriostatic action may occur in the spinal fluid of patients with meningococcic meningitis on treatment with sulfanilamide, the following experiments were carried out. Sulfanilamide was added in decreasing concentrations to specimens of the spinal fluid of patients prior to treatment. The spinal fluid–sulfanilamide mixtures were incubated at 37 C. It was found that sulfanilamide may either continuously inhibit or markedly delay the growth of meningococci in such spinal fluids, depending on the concentration of the drug. Further experiments showed that sulfanilamide is also bactericidal toward meningococci in spinal fluids of patients with meningococcic meningitis. Increase in the concentration of sulfanilamide and in the time of exposure of the meningococci in the spinal fluid to the action of the drug results in an increase in bactericidal activity. In order to elucidate whether or not leukocytes present in such spinal fluids play an essential role in this activity of sulfanilamide toward meningococci, similar experiments were carried out, employing spinal fluids of patients free of meningitis who had received sulfanilamide by mouth. It was found that even in the absence of an increased number of leukocytes sulfanilamide may cause loss of viability of the micro-organisms. It should be emphasized, however, that no conclusions may be drawn from these experiments as to the extent to which leukocytes contribute to the sterilization of spinal fluids of patients with meningococcic meningitis.

An analysis was made of the pertinent data on all patients with meningococcic meningitis admitted to the Children's Hospital since 1933. The results obtained in serum-treated patients were compared with those in patients treated with sulfanilamide either alone or in conjunction with serum. Antimeningococcic serum was administered intrathecally in 15 to 20 cc. amounts twice daily until the patients improved and cultures of the spinal fluid became sterile. Sulfanilamide was given by mouth in an average twenty-four hour dose of 2 to 2½ grains (0.13 to 0.16 Gm.) per pound of body weight. As improvement occurred, the twenty-four hour dose was reduced to 1 grain (0.064 Gm.) per pound of body weight. In a number of cases, 0.8 per cent sulfanilamide in physiologic solution of sodium chloride was given intrathecally in 15 to 20 cc. amounts once daily until the spinal fluid became sterile. Neter, Weintraub and Dayman showed that intrathecal administration of sulfanilamide to patients free of meningitis resulted in relatively high concentrations of free sulfanilamide (10 to 15 mg. per hundred cubic centimeters) in the spinal fluid within a few hours; the concentration of the drug in the spinal fluid markedly decreased within eighteen hours. Parallel determinations of the level in the blood revealed only low concentrations (1 mg. or less per hundred cubic centimeters). It is concluded from these experiments that it is advisable to give the drug also by mouth in order to obtain suitable concentrations in the blood and tissues.

Of 23 successive patients with meningococcic meningitis (1933-1937) treated without sulfanilamide, 6 died. Of 21 adequately treated patients (for twenty-four hours and longer), 4 died. Of 26 successive patients (1937-1939) treated with sulfanilamide, 7 died. When inadequately treated patients are excluded, there were 2 deaths in 21 cases. Although no final conclusions can be drawn from this small series, the reduction in mortality seems to indicate the efficacy of sulfanilamide in meningococcic meningitis. This impression is further substantiated by the following observations: 1. The clinical recovery appeared to be more rapid in sulfanilamide-treated than in non-sulfanilamide-treated patients. 2. The spinal fluid usually became free of micro-organisms (both by microscopic examination and by culture) on the second or third day in the sulfanilamide-treated group, as compared with the fifth or sixth day in the non-sulfanilamide-treated group. 3. The period of hospitalization for the sulfanilamide-treated group averaged nineteen days, whereas that for the non-sulfanilamide-treated group averaged twenty-five days. 4. Infants seriously ill with meningococcic meningitis

unexpectedly recovered, and a patient of Dr. Douglas P. Arnold, an infant 10 weeks old, included in this group, recovered from a recrudescence of meningitis when treated with sulfanilamide only. 5. A patient seriously ill with meningitis due to infection with the type 2 meningococcus, who failed to respond to large amounts of serum, recovered following treatment with sulfanilamide. It is interesting to note that in this series sulfanilamide failed to reduce the incidence of complications, such as hydrocephalus, panophthalmitis, uveitis, otitis media and deafness.

Significance of Bronchial Obstruction in Pulmonary Tuberculosis in Children and Its Relation to Epituberculosis. K. L. TERPLAN.

The close interdependence of occlusion of bronchial tubes by tuberculous granulation tissue and lobar or lobular atelectasis in the course of primary tuberculosis in children is demonstrated by the postmortem observations in 5 cases. In 2 of these cases recent stages were found, with massive caseated endobronchial tuberculosis and complete atelectasis of the corresponding lobules. In 2 others there were calcified lesions within the lumens of third order bronchi, representing healed states of Ghon foci, and additional calcified and ossified endobronchial lesions in close relation to the primary foci. The corresponding lobules showed old collapse induration with funnel-like retraction of the pleural surface. In the fifth case the condition was clinically diagnosed as epituberculous pneumonia of the upper lobe of the right lung and was observed over several years, until shortly before death, by means of a series of roentgenograms. Post mortem, extreme collapse induration was found, with unusual shrinkage of the entire upper lobe of the right lung, due to calcific occlusion of its main bronchus. In an instance of a typical epituberculous pneumonic shadow in a child 3 years of age, soft foreign particles were expectorated from the bronchus leading to the involved lung during bronchoscopic examination. These proved microscopically to be caseated lymph node structures containing tubercle bacilli. The child's subjective condition became normal within a few days. The massive shadow has decidedly cleared up in the course of three months. The anatomic findings presented here do not support the view that epituberculosis is true tuberculous pneumonia which heals by resolution. They confirm in part the view stressed by Rössle that atelectasis is the anatomic substrate of so-called epituberculous pneumonia. This atelectasis was caused by complete obturation of bronchial lumens by specific tuberculous structures. A complete report will be published in the *American Review of Tuberculosis.*

Intermediate Streptococcus-Pneumococcus Strains. ERNEST WITEBSKY and HELEN WARD.

While it is an established fact that pneumococci of one type may be transformed into pneumococci of another type by several procedures, most of the authors doubt that a streptococcus might be transformed into a pneumococcus or vice versa. Rough strains of pneumococci resembling streptococci nevertheless might be classified as pneumococci though their type specificity is lost. Occasionally pneumococci are isolated that are difficult or impossible to type. On the other hand, it is known that a carbohydrate characterizing a specific type of pneumococcus might have its counterpart in an entirely different species of micro-organism.

We recently isolated a gram-positive coccus in chains from the blood stream of a patient who gave a strong reaction with pneumococcus type III antiserum. The strain, however, could be identified as Streptococcus faecalis. It lost its property to react with type III antiserum after several weeks' subculturing. We want to describe now a strain that was isolated from the prostate of a patient. This strain when cultured in infusion broth forms large clumps that readily settle to the bottom of the tube. The supernatant fluid appears to be entirely clear.

The sediment, however, may be shaken up fairly evenly. On microscopic examination a gram-positive coccus forming long chains is observed. The strain agglutinates strongly in pneumococcus type XXIX antiserum. This holds true for diagnostic horse as well as rabbit serum. Immediate agglutination occurs, and some cross reaction with type XXI antiserum is observed. The strain appears to be only very slightly pathogenic in mice and is insoluble in bile. The growth of the strain is inhibited by optochin in concentrations up to 1:80,000 for three days. When the organism is cultured in 1 per cent dextrose broth, a p_H of 5.15 is obtained. There is no growth in 2 or 4 per cent saline broth. The strain does not ferment lactose and inulin, but it ferments several other sugars. When it is cultured on a blood plate, a slight zone of beta hemolysis is observed, with a predominance of greenish discoloration.

We are apparently dealing with an intermediate between the streptococcus and the pneumococcus group, and it seems to be difficult to decide whether or not this organism should be considered a streptococcus or a pneumococcus. One is inclined to label it as a streptococcus giving a cross reaction with pneumococcus type XXIX antiserum. However, a few of its properties do not fit into the streptococcus group either.

Book Reviews

Diverticula and Diverticulitis of the Intestine—Their Pathology, Diagnosis and Treatment. Harold C. Edwards, M.S. (London), F.R.C.S. (England), Surgeon and Lecturer in Surgery to King's College Hospital, London; Surgeon to the Evelina Hospital for Sick Children, London; Jacksonian Essayist of 1932 and late Hunterian Professor, Royal College of Surgeons of England. With foreword by Gordon Gordon-Taylor, O.B.E., M.S., F.R.C.S. Pages 335, with 223 illustrations, many in color. Price, $8. Baltimore: Williams & Wilkins Company, 1939.

A monograph may claim merit on one or more of several grounds. It may be the first of its kind on a given subject, it may tower above the others by completeness and thoroughness, by originality of ideas, by excellence of presentation or by appeal of its style. Any one of these qualities, even if present alone, may justify a new book, because only too often one is at a loss to find a single saving feature. It is indeed a rare experience to find all these virtues combined in one work. This is the case in the monograph of Edwards. The diagnostician, the roentgenologist, the surgeon and the pathologist will find in it all that is known on the subject. The pathologist will be especially interested in the chapters dealing with the incidence, the morbid anatomy, the pathogenesis and the etiology. The many reproductions of gross pathologic specimens and of microscopic slides, many of them in colors, are expertly done. Some phases of the origin of diverticula are far from settled. These are presented as such and the different opinions analyzed and evaluated. In four sections and in twenty-eight chapters the congenital diverticula and the diverticula of the duodenum, of the jejunum and of the colon are presented. The bibliography is impressive by its volume (12 pages), though it is limited to the four leading languages. The index is well organized and contains references to illustrations. The high quality of the paper, of the print and of the binding add to the enjoyment of this superb volume.

A Symposium on the Blood and Blood-Forming Organs. Pp. 264. Price, $3. Madison, Wis.: The University of Wisconsin Press, 1939.

In this book are collected all the papers read at the Institute for the Consideration of the Blood-Forming Organs held under the auspices of the University of Wisconsin Medical School, Sept. 4-6, 1939. E. Meulengracht, of Copenhagen, is the author of two chapters. The introductory chapter on some historical aspects of hematology refers to chlorosis, pernicious anemia and leukemia; a later chapter deals with some etiologic factors in pernicious anemia. C. J. Watson discusses the porphyrins and diseases of the blood. C. P. Rhoads's presentation on aplastic anemia is based on a study by the author and his associates of 97 cases of the disease, with 47 necropsies. C. W. Heath discusses anemia due to deficiency of iron. In the past six years he has seen in Boston at least 8 outstanding examples of true old-fashioned chlorosis. Apparently that disease is not quite as extinct as Meulengracht seems to think. The chapter on anemias due to nutritional deficiency is a 4 page abstract of a lecture by G. R. Minot. L. K. Diamond presents the erythroblastic anemias, with special emphasis on the so-called Mediterranean anemia and on fetal erythroblastosis. Hemolytic anemia is discussed by R. L. Haden, experimental leukemia by J. Furth, monocytic and subleukemic leukemia by C. E. Forkner, Hodgkin's disease by E. B. Krumbhaar, the reticuloendothelial system by C. A. Doan, the hematologic and pathologic aspects of infectious mononucleosis by H. Downey, polycythemia by P. Reznikoff, marrow cultures by E. E. Osgood and the present status of the problem of blood coagulation by H. Eagle. The outstanding feature of the articles is that they are not mere reviews but summaries of original work of their authors and that they give a personal interpretation of recent studies on the subjects under discussion. Some of the chapters are illustrated with photographs, drawings, charts and tables; some have bibliographies. The paper, the print and the binding are excellent. The book can be recommended without reservation.

Books Received

MEDICAL USES OF RADIUM. SUMMARY OF REPORTS FROM RESEARCH CENTRES FOR 1938. Medical Research Council, Special Report Series, no. 236. Paper. Pp. 49. Price, 30 cents. New York: British Library of Information, 1940.

SHOCK: BLOOD STUDIES AS A GUIDE TO THERAPY. John Scudder, M.D., Med. Sc.D., F.A.C.S. Cloth. Pp. 315, with 60 illustrations. Price $5.50. Philadelphia: J. B. Lippincott Company, 1940.

PNEUMOCONIOSIS (SILICOSIS). THE STORY OF DUSTY LUNGS. A PRELIMINARY REPORT. Lewis Gregory Cole, M.D., Director of Silicotic Research, John B. Pierce Foundation, New York. William Gregory Cole, M.D. Cloth. Various pagination. Price $1. New York: John B. Pierce Foundation, 1940.

THE ELECTROCARDIOGRAM IN CONGENITAL CARDIAC DISEASE. A STUDY OF 109 CASES, 106 WITH AUTOPSY. Maurice A. Schnitker, B.Sc., M.D., Associate Attending Physician, Toledo Hospital; Junior Staff Physician, Lucas County Hospital; Member Active Staff, St. Vincent's Hospital, Toledo, Ohio. Cloth. Pp. 147, illustrated. Price $3. Cambridge, Mass.: Harvard University Press, 1940.

STUDIES FROM THE DIVISION OF LABORATORIES AND RESEARCH, NEW YORK STATE DEPARTMENT OF HEALTH, AUGUSTUS B. WADSWORTH, M.D., DIRECTOR. COLLECTED REPRINTS, VOLUME IX, JANUARY 1937-JUNE, 1939. Paper. Various pagination.

"BREATHING MACHINES" AND THEIR USE IN TREATMENT. REPORT OF THE RESPIRATORS (POLIOMYELITIS) COMMITTEE. Medical Research Council, Special Report Series, no. 237. Paper. Pp. 90, with 13 illustrations. Price 60 cents. New York: British Library of Information, 1939.